COMPETITION AUTHORITY

COMPETITION AUTHORITY DECISION

File No : 2019-3-006 (Investigation)
Decision No: 21-04/52-21
Date of Decision : 21.01.2021

A. BOARD MEMBERS IN ATTENDANCE

Chairman : Birol KÜLE
Members : Arslan NARİN (Deputy Chairman), Şükran KODALAK, Hasan Hüseyin ÜNLÜ, Ayşe ERGEZEN

B. RAPPORTEURS: Emin Cenk GÜLERGÜN, Cansu TOPAK KORKMAZ, Dilara Nur CANSU ISLAM, Muhammad Ali BEKTEMUR

C. APPLICANTS : - Atty. Mustafa Ali ERDOST
Sezenler Cad. No:12/7 Sıhhiye Çankaya/Ankara

D. UNDER INVESTIGATION: - Novartis Sağlık Gıda ve Tarım Ür. San. ve Tic. A.Ş.
Representative: Atty. Turgan GÜRMEN
Akat Mah. Meydan Cad. Meydan Apt. No:6/9 Beşiktaş/İstanbul

- Roche Müstahzarları San. A.Ş.
Representatives: Atty. İlmutluhan SELÇUK, Atty. Artun ATAK
Ebulula Mardin Cad. No:57 Akatlar Beşiktaş/İstanbul

(1) **E. SUBJECT OF THE FILE: The claims that Novartis Sağlık Gıda ve Tarım Ürünleri San. ve Tic. A.Ş. and Roche Müstahzarları San. A.Ş. violated Article 4 of Act No. 4054 in order to increase the use of Lucentis, which is the more expensive of the two drugs, Altuzan and Lucentis, used in eye diseases.**

(2) **F. SUMMARY OF THE CLAIMS:** In summary, the application made to the Competition Authority (Authority) with the letter dated 22.01.2019 and numbered 401 states

- The drug named *Altuzan* (*Avastin*)[1] with the active ingredient *Bevacizumab*, licensed by Roche Müstahzarları Sanayi A.Ş. (ROCHE) in 2005 to be used in the treatment of metastatic cancers, can also be used by ophthalmologists in the treatment of age-related macular degeneration (AMD) by injection into the eye, 100 mg box of the product in question is sold at a price of 938.85 TL and one box is sufficient for 10-20 doses,

- Lucentis has been sold by Novartis AG since 2008, the sale price of 10 mg of the product is 2.701.29 TL, this drug is used by injection into the eye for the treatment of AMD, one box of medicine is sufficient for a single dose,

- Roche AG and Novartis AG companies have derived unfair profits by engaging in cartel activities in order to increase the use of Lucentis, which is the more expensive of the two drugs called Altuzan and Lucentis used in eye diseases,

- When the sales prices and mg values of both drugs and how many doses can be used according to those are compared, it is seen that Lucentis is 30-40 times more expensive than Altuzan,

[1] The product, which is sold with the name Avastin out of Turkey, was launched in Turkey with the name Altuzan. In the decision, the names Avastin and Altuzan are used to refer to the same product

- The use of Lucentis for the treatment of AMD is within indication[2]; Altuzan, on the other hand, is used off-label, its off-label use is regulated according to the Ministry of Health's Off-label Use of Drugs Guide,

- For the drugs specified in the Off-Label Drugs List (OLDL) that can be used without the additional approval of the Turkish Medicines and Medical Devices Agency (TMMDA) in the aforementioned Guide, the drug can be used by the physician without the need to make a request to the Turkish Medicines and Medical Devices Agency,

- Bevacizumab, the active ingredient of Altuzan, is included in this list, so the use of Altuzan in the treatment of AMD is legal.

The information submitted by the applicant regarding the allegation that the undertakings formed a cartel, in summary, is as follows;

- With the decision[3] of the Italian Competition Authority (ICA) dated 27.02.2014, it was found that Roche AG and Novartis AG made an illegal agreement with their Italian subsidiaries in violation of Article 101 of TFEU[4],

- Following a complaint by an association of private health clinics and the Italian Society of Ophthalmology, the case started upon the allegation that Roche AG and Novartis AG acted together to block the use of Avastin in order to gain a commercial advantage over the much more expensive drug Lucentis,

- Genentech Inc. (GENENTECH), a subsidiary of the Roche Group developed Altuzan and Lucentis; GENENTECH retains its commercial rights of Altuzan and Lucentis drugs in the United States (USA); licensed the aforementioned undertakings for the purpose of licensing Altuzan on behalf of ROCHE for use in cancer treatment and Lucentis on behalf of NOVARTIS for use in AMD treatment, in countries other than the USA,

- The European Medical Agency (EMA) approved Altuzan in 2005 for use in cancer treatment and Lucentis in 2007 for use in AMD treatment by injection into the eye,

- Long before Lucentis was approved, the off-label use of Altuzan in the treatment of AMD by intraocular injection became widespread,

- Due to the price difference between Lucentis and Avastin, Italian National Health System uses Altuzan instead of Lucentis to treat AMD and other eye diseases.

- After Lucentis was licensed, the off-label ophthalmic[5] use of Altuzan began to decline,

- Roche AG has not obtained a license for Altuzan for ophthalmic applications although studies supporting the efficacy of Altuzan in the treatment of AMD have increased,

- In June 2011, Roche AG requested EMA to change the Summary of Product Characteristics, which is the official document containing all the information regarding Altuzan, and in this request -in order to direct the relevant physicians to Lucentis- Roche AG applied for the addition of a sentence stating the ophthalmic risks of the drug, to Altuzan's package insert,

---

[2] Indication can be defined briefly as diseases or conditions in which a drug can be used. The treatment methods to be followed for any disease and the course of the treatment process are determined within the framework of the indication

[3] Autorità Garante della Concorrenza e del Mercato, decision no. 24823, proceedings I760 *Roche-Novartis/Farmaci Avastin e Lucentis*, 27.02.2014.

[4] Treaty on the Functioning of the European Union.

[5] It is used in medicine to mean "relating to the eye".

- However, EMA did not allow an official warning to be sent to physicians; besides, detected the systemic risks that were not written on Lucentis and made changes in the summary of product characteristics for both products,

- ICA launched an investigation against Novartis AG, Roche AG, GENENTECH, Novartis Farma S.p.A. (Novartis Italy) and Roche S.p.A. (Roche Italy) in February 2013, detected an anti-competitive agreement between Roche AG and Novartis AG, at the same time the market shares arising from off-label use of Lucentis and Altuzan were 50% and 40%, respectively,

- ICA found that Roche AG and Novartis AG intended to raise and disseminate concerns about the safety of ophthalmic use of Altuzan to increase sales of Lucentis -in line with their own benefit expectations-,

- According to the final decision of the authority; in the e-mail correspondence between the chief executive officers (CEO) of the Italian subsidiaries of Roche AG and Novartis AG, the artificiality of the product differentiation that emerged with the change of Avastin's summary of product features was mentioned, independent studies to this end were funded by Novartis AG, safety concerns were generated and disseminated about Avastin's use in eye diseases in collaboration with patient groups,

- Novartis AG's internal documents declared that ophthalmologist feeling safe while using Avastin was a risk to the company, there were statements that the impact of independent comparative studies submitted against Lucentis was successfully minimized by companies,

- By means of Lucentis sales, Novartis AG made a gain directly through sales and indirectly through its Roche AG shares, and Roche AG made a gain indirectly within the scope of copyrights through its subsidiary GENENTECH; this has developed a mutual interest relationship,

- Considering June 2011, when attempts were made to change the medicine package insert, as the starting date of the violation, ICA fined Novartis AG with an administrative fine of 92.028.750 Euros and Roche AG with an administrative fine of 90.593.369 Euros,

- In the Turkish market, the drug named Altuzan is used in the treatment of AMD off-label, its off-label use within the scope of the Off-Label Use of Drugs Guide (OLD Guide) is legal,

- Roche Müstahzarları Sanayi A.Ş. (ROCHE) submitted the application with the same content as the application made to EMA to TMMDA on 29.11.2016,TMMDA accepted the application[6],

- Thus, false information that would increase the concerns of physicians and patients was added to Altuzan's package insert, with the information added to the package insert, the patients are anxious that the intraocular use of Altuzan causes significant side effects, when there is a problem related to the use of Altuzan, the patients blame the physicians, physicians, on the other hand, are concerned that if they use Altuzan and then the patient's health is adversely affected, they will be exposed to malpractice lawsuits -due to the explicit warning in the package insert information.

- Turkish Ophthalmology Association (TOA) represents ophthalmologists in Turkey, this association is the only association that has a say in the relevant field,

[6] In the investigation, it was found that the main application was made on 29.12.2011 and it was approved by TMMDA on 30.05.2014.

TOA organized seminars for ophthalmologists across the country, stated that Lucentis should be used instead of Altuzan in seminars, suggested that if Altuzan was used, malpractice lawsuits might be filed, sponsors of these seminars have been Novartis Sağlık Gıda ve Tarım Ürünleri San. ve Tic. Inc. (NOVARTIS),

- Physicians who are competent in their fields and oppose the aforementioned actions in TOA were forced to be passive,

- Pharmaceutical representatives made suggestions for the use of Lucentis and increased the concerns of physicians for Altuzan,

- Lucentis is included in the drug reimbursement system with the Health Implementation Communique (HIC) of the Social Security Institution (SSI); however, even if Altuzan is cheaper, it is not within the scope of reimbursement,

- All these implementations facilitated the cartel activities of ROCHE and NOVARTIS companies,

- According to the Comparison Study of Age-Related Macular Degeneration Treatment Trials in the USA (CATT Study) and the Alternative treatments to inhibit VEGF in age-related CNV Study (IVAN Study) in the UK, as well as the report accepted by the scientific committee of EMA in 2012, Altuzan and Lucentis' safety and efficacy profiles are equivalent.

(3) **G. PHASES OF THE FILE:** The Initial Examination Report, dated 31.01.2019 and numbered 2019-3-06/II, which was prepared upon the said application, was discussed at the meeting of the Competition Board (Board) dated 13.02.2019 and the decision numbered 19-07/89-M was taken to conduct a preliminary inquiry in accordance with the first paragraph of Article 40 of the Act No. 4054 on the Protection of Competition (Act No. 4054).

(4) During the preliminary inquiry phase, on-site inspections were made at NOVARTIS and ROCHE company headquarters on 07.05.2019 and information was requested from the undertakings. In this context, the reply letter sent by NOVARTIS dated 20.05.2019 and no 3364, and the reply letter sent by ROCHE dated 20.05.2019 and no 3375 were saved in the Authority’s records. Preliminary inquiry report dated 10.06.2019 and numbered 2019-3-006/ÖA which was prepared as the result of the examinations was discussed at the Board meeting on 13.06.2019 and it was decided to launch an investigation against NOVARTIS and ROCHE with the number 19-21/307-M pursuant to Article 41 of Act No. 4054.

(5) On 24.06.2019, pursuant to the second paragraph of Article 43 of Act No 4054, the parties were notified that an investigation was launched and they were requested to submit their first written plea within 30 days. The first written pleas of the parties were submitted to the Authority's records within the legal period.

(6) The Information Note numbered 2019-3-006/BN-01 prepared on 12.11.2019 on the extension of the investigation period was discussed at the Board meeting dated 14.11.2019 and the Decision numbered 19-40/641-M was taken to extend the investigation period for six months.

(7) The petition, which was sent in addition to the first written plea made by ROCHE, and which includes the correspondence between TMMDA and the General Directorate of Public Hospitals (GDPH) and ROCHE, and the news in the media regarding the patients who suffered from vision loss as a result of the intravitreal use of *Altuzan* was submitted to the records of the Authority with the number 3021 on 27.03.2020.

(8) Within the scope of the investigation; information was requested from the Association of Research-Based Pharmaceutical Companies (AIFD) and TOA with the date 20.04.2020 number 5656 and with the date 29.04.2020 with the number 5821, from ROCHE with the date 20.04.2020 and number 5654, from NOVARTİS with the date 20.04.2020 and number 5653, from Bayer Türk Kimya San. Ltd. Ltd. Şti. (BAYER) with the date 27.04 .2020 and number 5652, and with the date 29.04.2020 and number 5822, from Sanofi Sağlık Ürünleri Ltd. Şti. Ltd. Şti. (SANOFI) with the date of 27.04.2020 and number 5754, from Allergan İlaçları Tic. A.Ş. (ALLERGAN) and IQVIA Tıbbi İstatistik Ticaret ve Müşavirlik Ltd. Şti. (IQVIA) with the date 27.04.2020 and number 5766, and with the date 28.04.2020 and number 5817, and the relevant answers were submitted to the records of the Authority on various dates.

(9) Besides, in order to better understand the usage areas and frequencies, treatment methods and treatment efficacy of the products applied in the treatment of diseases that are similar to those treated with the drugs named *Altuzan* and *Lucentis*, which are directly related to the subject of the investigation, and to determine what kind of change the HIC amendment made on 28.12.2018 caused in the use of these drugs, information was requested (.....)on 04.05.2020, and the relevant answers were submitted to the Authority's records on various dates.

(10) In addition to these, in order to obtain information about the correspondence between TMMDA, SSI, and the parties to the investigation regarding the HIC amendment dated 28.12.2018, and about the lawsuits filed against this HIC amendment and medicine for human use, information was requested from TMMDA with the number 6118 on 08.05.2020, from SSI with the number 6119 on 08.05.2020., and with the number 6942 on 03.06.2020, and with the number 6882 on 02.06.2020, and the relevant answers were submitted to the Authority's records on various dates.

(11) Ultimately, on 04.06.2020, information was requested from ROCHE with the number 6994, from NOVARTIS with the number 6993, and AIFD with the number 6997. Besides, the letter sent by the complainant was submitted to the Authority's records with the number 5558 on 09.06.2020.

(12) The Investigation Report, dated 15.06.2020 and numbered 2019-3-6/SR-01, which was prepared at the end of the investigation phase, was received by the attorney of NOVARTIS on 17.06.2020. The Investigation Report dated 15.06.2020 and numbered 2019-3-6/SR-02 was also received by the ROCHE attorney on 17.06.2020.

(13) For the second written pleas to be prepared by the undertakings, a request was made to extend the defense period up to one fold pursuant to Article 45 of the Act No 4054. With the Board's decisions dated 09.07.2020 and numbered 20-33/423-M and 20-33/424-M, the second written plea period of the parties was extended by 30 days, and the second written pleas of the aforementioned undertakings were submitted to the Authority's records on 17.08.2020.

(14) Additional Opinions dated 15.09.2020 and numbered 2019-3-6/EG-01 (NOVARTIS), and 2019-3-6/EG-02 (ROCHE), prepared within the framework of the parties' second written pleas, were conveyed to the members of the Board and the relevant undertakings.

(15) The third written pleas of the parties, which were sent following the Additional Opinion, were submitted to the Authority's records by NOVARTIS on 16.11.2020 with number 12335, and by ROCHE on 16.11.2020 with the number

12323.

(16) The issue of holding an oral hearing pursuant to Article 46 of the Act No. 4054 was discussed at the Board meeting on 03.12.2020 and the decision dated 12.01.2021 and numbered 20-52/727-M was taken to hold the hearing online. An oral hearing was held on the aforementioned date.

(17) The Board rendered the final decision numbered 21-04/52-21 on 21.01.2021, based on the Report, Additional Opinion, collected evidence, written pleas, the hearing and the file contents regarding the investigation conducted.

(18) **H. RAPPORTEUR OPINION:** The relevant Report and the Additional Opinion state the following:

- NOVARTIS and ROCHE's deterring the use of Altuzan by acting in harmony and directing the administrative or judicial processes with misleading information by emphasizing the risk of endophthalmitis and side effects of Altuzan, in a way that will shift the demand to Lucentis in the treatments applied intraocular, the aforementioned undertakings' attempt to create a perception of difference that does not reflect the truth that Altuzan and Lucentis are different and their making negative publicity about Altuzan to doctors violate Article 4 of the Act No. 4054,

- NOVARTIS and ROCHE cannot benefit from exemption within the scope of Article 5 of Act No. 4054,

- Administrative fines must be imposed on NOVARTIS and ROCHE pursuant to the Article 16 of Act No. 4054.

I. EXAMINATION, GROUNDS AND LEGAL BASIS

I.1. Parties under Investigation

I.1.1. Novartis Sağlık Gıda ve Tarım Ürünleri San. ve Tic. A.Ş. (NOVARTİS)

(19) Novartis AG, a multinational holding company, operates in six areas: pharmaceuticals, eye health, generic drugs, animal health, consumer health, and vaccines. Novartis AG continues its activities in Turkey through NOVARTIS.

(20) NOVARTIS is a (.....)% subsidiary of Novartis Pharma AG, Novartis Pharma AG is a (.....)% subsidiary of Novartis International Pharmaceuticals AG., and (.....)% of the shares of Novartis International Pharmaceuticals AG is owned by Novartis AG, the holding company of the Novartis Group.

(21) Currently, NOVARTIS has three main fields of activity: pharmaceuticals, vaccines and consumer health. Consumer health products consist of the over-the-counter drugs and the animal health sub-divisions.

(22) Novartis AG holds a non-controlling minority stake in Roche AG in Switzerland, the holding company of the Roche Group. According to the information provided by the representatives of the undertakings, Novartis AG holds (.....)% of the voting shares. When the non-voting shares are taken into account, the shares held by Novartis AG correspond to (.....)% of Roche AG's capital. Therefore, the share of Novartis AG in the distributable net profit of Roche AG is (.....)%. In addition, it is stated that Novartis AG's minority stake in Roche AG is not of a nature to directly or indirectly affect the activities of the Roche Group and that both groups are completely independent from each other, and this has been confirmed in the *Novartis/Chiron*

decision of the European Commission[7]

I.1.2. Roche Müstahzarları Sanayi A.Ş. (ROCHE)

(23) Roche AG is the ultimate parent undertaking of the Roche Group companies and its shares are registered on the SIX Swiss Exchange in Zurich. Roche AG, established under Swiss laws, carries out the production and marketing of all kinds of chemical medicines for human use and active pharmaceutical ingredients, beauty preparations, veterinary products, agrochemicals and pesticides, feed vitamins, nutritional essences and fertilizing materials.

(24) Roche AG is controlled by a group of members, many of whom are mainly members of the Hoffman and Oeri families, who are the founders of the Roche Group. Members of the Hoffmann and Oeri families hold (.....)% of the voting shares in Roche AG. Pursuant to the contract signed and became effective in 1948, this group of shareholders jointly exercise their voting rights in proportion to their shares. Maja Oeri, a former member of this shareholder group, currently holds (.....)% of the voting rights in Roche AG and can exercise her voting rights independently.

(25) Between 2001 and 2007, Novartis AG purchased (.....)% of the voting shares of Roche AG. When the non-voting shares are taken into account, the shares held by Novartis AG correspond to (.....)% of Roche AG's capital. However, (.....)% of the company's capital consists of non-voting shares.

(26) Other shares of Roche AG are held by minor shareholders, except those owned by Hoffmann and Oeri families, Maja Oeri and Novartis. Novartis AG has no control over Roche AG through the shares it owns, and Roche AG is under the control of the Hoffmann and Oeri families.

(27) The following is the partnership structure of Roche AG:

Table 1-Roche AG's Partnership Structure

Shareholders	Rate
Roche Holding Ltd	(.....)
F. Hoffmann-La Roche Ltd	(.....)
Roche Finanz AG	(.....)
Biopharm AG	(.....)
Phaor AG	(.....)
TOTAL	100.000
Source: Information from the Undertaking	

(28) Roche Group has three subsidiaries in Turkey:

(i) ROCHE

(ii) Roche Diagnostics Turkey A.Ş.

(iii) İnfogenetik Molekuler Bilgi Hizmetleri A.Ş. (İNFOGENETİK)

(29) ROCHE is the local company of the Roche Group responsible for the marketing, sales and distribution of medicinal preparations for human use in Turkish markets. It is stated that INFOGENETIK, in which ROCHE has a (.....)% stake, does not have any activity in the sale and distribution of medical preparations.

I.2. Information and Documents Obtained from Undertakings,

[7] COMP/M.4049, Novartis/Chiron, 06.02.2006, para. 28

Associations of Undertakings Hospitals and Public Institutions[8]

(30) Within the scope of the file, on-site inspections were carried out at NOVARTIS and ROCHE premises during the preliminary inquiry and investigation process, and information was requested from the parties as well as from IQVIA, BAYER, ALLERGAN, SANOFI, AIFD, TOA, some public and private hospitals providing eye treatments, and the relevant public authorities, SSI and TMMDA. The findings regarding the information and documents obtained in this way are given below.

I.2.1. NOVARTİS

I.2.1.1. Documents from On-Site Investigation

I.2.1.1.1. Documents Regarding Objections Made to Public Institutions

(31) In the e-mail sent from AIFD Health Policy Director (.....) to ALLERGAN, BAYER, ROCHE and NOVARTIS officials on 28.01.2019, it was stated that the opinion of TOA was received regarding the amendment made on HIC on 28.12.2018 (Document 7). The following statement was included in the opinion attached to the said e-mail;

"As is known, Ranibizumab (Lucentis, Novartis) and Aflibercept (Eylea, Bayer) are licensed anti-VEGF products that can be used intravitreally in our country. Bevacizumab (Altuzan, Roche), on the other hand, is not a licensed product, and there is the phrase "not suitable for intravitreal use" in its package insert. In other words, in addition to being an off-label drug, the potential risks of intraocular use are emphasized."

The last paragraph of the text contains the following statement:

Turkish Ophthalmology Association Central Administrative Board received the opinion of the 3 related units (Medical Retina, Vitreo-Retinal Surgery and Uvea-Behçet Units) on the aforementioned news and, in almost complete agreement, according to these assessment, the units stated that bevacizumab is an effective product, although it is not as much efficient as the licensed products and there are differences between the diseases specified on the communiqué in terms of effectiveness, that the sentence in the communiqué regarding the conditions where bevacizumab is contraindicated, specified in the treatment algorithms is not clear, that due to the lack of compounding pharmacy for the division of the drug in Turkey, and in order to reach the dose (1.25 mg/0.1 ml, this was later institutionally corrected to 1.25 mg/0.05 ml.) specified on the communiqué , the drug should be diluted twice after dividing, and this would cause patient and physician risks, especially in terms of endophthalmitis risk, which is a safety problem, and that it will make the operating room conditions, which are already intense in institutions providing tertiary health care, more difficult and create a blockage in terms of functionality. Our units also found the articles 4.2.33 -A, B, C and D of the communiqué, which gives application algorithms for 4 diseases, extremely contrary to current scientific treatment approaches."

(32) The following was stated in the petition addressed to SSI (Document 7), which is attached to the e-mail titled "FW: SSI objection petition" sent on 09.01.2019 from (.....) NOVARTIS Country Legal and Compliance Director, to (.....), NOVARTIS

[8] The documents in the findings were included in their original form, typographical errors and expression errors were preserved in the original text of the decision in Turkish.

Country Pharmaceutical Development Coordinator:

"Bevacizumab is not approved for use in eye diseases and there is no clinical trial for use in the eye regarding it. Reimbursement of the active substance Bevacizumab as mandatory first-degree treatment is illegal while there are products containing active substances approved for eye diseases, whose safety is proven with clinical trials, and this poses serious risks to the health of the patient for the reasons explained below:"

The alleged risks are:

(i) It is Contrary to the Legislation to Accept the Active Substance Used Off-Label as Mandatory First-line Treatment Since It Has No Clinical Trial And License Approval For Ophthalmology

(ii) Public Health Risks and Examples from Real Cases in Other Countries

(iii) The Regulation Set Out at Article 4.2.33 of HIC, is Contrary to the Regulation on Medical Deontology and Causes Professional Liability Risks for Physicians"

After examining the risks under these main headings, it is stated that the action taken to amend the Article 4.2.33. of HIC poses a danger to public health and patient safety, and it is requested that the administrative action be removed immediately. It is stated that if no action is taken by SSI in this direction, legal remedies will be saught for the suspension and cancellation of this regulation, which allows the intravitreal use of products with active substance *Bevacizumab*, the use of which poses a serious health risk for patients in the treatment of eye diseases.

(33) In the first of the e-mail attachments sent from AIFD Health Policy Director (.....) to the officials of ALLERGAN, NOVARTIS, BAYER and ROCHE on 28.02.2019, there is a petition dated 19.02.2019 addressed to the General Directorate of SSI General Health Insurance by AIFD. The petition includes the following statements:

"(…) Non-individual, systematic off-label use of drugs causes many legal uncertainties and illegalities in terms of drug legislation, especially drug-related responsibilities. (…)"

Possible negative aspects were examined under the headings of "1. In terms of drug legislation" and "2. In terms of patient rights".

Finally, it was requested that the sub-clauses titled

"4.2.33.A – Principles of use of drugs used in the treatment of neovascular age-related macular degeneration

4.2.33.B - Principles of use of drugs in retinal vein occlusion and central retinal vein occlusion

4.2.33.C- Principles of use of drugs in the treatment of visual impairment caused by choroidal neovascularization (CNV) due to pathological myopia (PM)

4.2.33.D – Principles of use of drugs used in the treatment of visual impairment caused by diabetic macular edema (DME)"

of Article 4.2.33. of HIC titled "Principles of drug use in eye diseases" be re-evaluated and cancelled.

(34) In the second attachment of the same e-mail, there is a reply letter dated

20.02.2019 addressed to AIFD from the General Directorate of SSI General Health Insurance. The letter includes the following statement:

"(…) The list of drugs to be paid for by our institution is determined within the framework of the decisions taken by the "Medical and Economic Evaluation Commission" and the "Payment Commission". In the commissions, there are the representatives of the Presidency of Strategy and Budget, Ministry of Treasury and Finance and the Ministry of Health, together with the officials of our Institution, and work and transactions are carried out by taking into account the opinions of academic specialist physicians… Health Implementation Communique regulations were also made within this framework".

I.2.1.1.2. Other Documents

(35) The following statement was included in the e-mail titled "RE: SSI petition of objection" sent on 08.01.2019 from (.....), NOVARTIS Ophthalmology Business Unit Director, to (.....), NOVARTIS Country Legal and Compliance Director:

"b.How can we include that the part "the preparation of the drug" in HIC increases the possibility of endophthalmitis by creating a risk of contamination, and that when this risk is completely inflicted on the person who prepared it, the physician will get into a difficult situation in matters such as malpractice?"

(36) In the 14th paragraph of the Word file titled "Süleyman Kaynak's recommendation Letter on Avastin" taken during the on-site inspection, the following statement was included regarding the use of the drug in the USA:

"Secondly, this molecule wasn't produced for intraocular use, and it is unlicensed for intraocular use all over the world and is used with off-label status in some countries. One of these countries is the United States. In the USA, there are two reasons for the prevalence of this use. Firstly, Supreme Court of the US issued a case law legalizing the use of unlicensed drugs. Based on this case law, use of drug remains within the framework of the legal connection between the patient and the physician (5). In this circumstance, especially private insurance companies in the healthcare system in the United States tend to agree more frequently and easily with physicians who provide more affordable patient services while making agreements with physicians, forcing physicians to provide services at lower prices in services including drugs."

(37) The following statement was included in the e-mail with the subject "Re: Vienna ASRS 2015 medical notes about the use of avastin in Trabzon KTu" sent from NOVARTIS Medical Manager (.....) to NOVARTIS Retina Product Specialist (.....) on 03.09.2015:

"During the bilateral visit we made at Trabzon KTU Medical Faculty this week, I mentioned that they use around 100 Avastins per month. Considering the data you shared, you emphasized that there are 27 cases of endophthalmitis in Mexico. How can we share this data with our clinicians, since it is an internal report."

(38) The following statement was included in the e-mail titled "Kayseri Erciyes University PFS *Ranibizumab* safety and efficacy presentation" sent from NOVARTIS Regional Medical Director (.....) to NOVARTIS Regional Medical Director (.....):

"Today, we had the opportunity to explain the efficacy, safety and advantages of PFS to 20 of our physicians at the presentation we made at Erciyes University. After the presentation, some of the main objections from some of our physicians were

as follows;

1- The Ministry was late in this decision, we were already applying bevasizumab, I underlined that the decision of the Ministry on this issue is about an off-label drug. I mentioned that SSI applications and drug indications were given by different ministries. I said that the physician's right to make a choice in treatment is being interfered with. One of our physicians said that the indication is not necessary ! that if there are sufficient clinical studies, he can be satisfied and that there are some studies done with bevasizumab. In this sense, I said, if you are convinced by clinical studies, Ranibizumab has done the most studies, and Ranibizumab has provided the most satisfaction in clinical efficacy and safety.

2- If we do the same thing, whose treatment expenses for the state are too high, with bevasizumab at a lower cost, why shouldn't we do it? I showed that Bevasizumab cannot be divided adequately even with compound pharmacy, it causes endophthalmitis in 1 patient in 2000; this risk is 1 in 40000 patients in PFS Ranibizumab. I showed that the costs and cases of endophthalmitis weren't recorded adequately in our country with examples from studies conducted abroad (France and USA). I asked how effectively and safely you can divide in a country where compound pharmacy is not active and would you do this to your relatives?

3- There are studies showing that the effectiveness of bevasizumab is almost as high as ranibizumab. Thereupon, I showed the DERBI study conducted in Israel as an example, and showed that patients with DME who worsened after bevasizumab were cured by ranibizumab treatment.

4- I know that in the CATT Study, Bevasizumab did not show so many side effects. I told this physician that s/he should not compare Bevasizumab, which was prepared sterile under clinical study conditions, with Bevasizumab, which was randomly divided in our clinics under unhygienic conditions. I stated that despite this, gastrointestinal bleeding was high in the Bevasizumab group in the first 2 years and that it was not as effective as ranibizumab in the PRN arm.

One of our physicians stated that local pharmaceutical companies may be beneficial to the country's economy in this respect. I said that local pharmaceutical companies are in a race with compound pharmacy to divide Bevasizumab instead of doing R&D studies based on the decision taken and showed the publication indicating that the exact division of bevasizumab at equimolar concentrations into injectors was not achieved in compound pharmacy, as well.

One of our board physicians (Prof) stated that he recently used Bevasizumab because of necessity, but s/he experienced a case of endophthalmitis 5 days later, and he found the remedy when he applied Ranibizumab treatment. (Defensive questions suddenly stopped)

It was a very nice meeting in every sense, I would like to thank (.....), especially Mr. (.....), for the excellent organization. There was a scientific sharing about why physicians would prefer PFS ranibizumab professionally."

(39) The following statement was included in the e-mail with the subject "About Bevacizumab" sent on 12.10.2018 from NOVARTiS Regional Medical Manager(.....) to (.....), NOVARTIS Ophthalmology Business Unit Director, and some NOVARTIS employees:

"*Hello,*

I did a pubmed search on the hot topic on Bevacizumab. Especially in some articles (2017-2018) from developing countries, there are explanations that the use of

Bevacizumab is cheap and the risk of endophthalmitis development is similar to other anti-VEGFs if applied in appropriate sterile conditions. The ministry may be trying to get support from such publications. At the bottom, you can find links to the articles I mentioned.

https://www.ncbi.nlm.nih.gov/pubmed/28724817
https://www.ncbi.nlm.nih.gov/pubmed/28724808
https://www.ncbi.nlm.nih.gov/pubmed/30127831
https://www.ncbi.nlm.nih.gov/pubmed/30069864
https://www.ncbi.nlm.nih.gov/pubmed/29437495
https://www.ncbi.nlm.nih.gov/pubmed/29380769
https://www.ncbi.nlm.nih.gov/pubmed/29217032
https://www.ncbi.nlm.nih.gov/pubmed/28099318 "

But in clinical trials and clinical experiences, the situation is the opposite, and I also send the related articles to you in the appendix. Considering the conditions in Turkey, adding Bevacizumab to HIC and putting it into routine use will bring along many problems."

(40) The following statement was on page 4 of the presentation in the e-mail attachment of "FW: March 2019 ministry presentation draft - medical part" sent from NOVARTiS Marketing Access Manager (.....) to NOVARTIS Marketing Access Director (.....) on 06.03.2019:

"It was published that in Israel, where bevasizumab is used, the experienced side effects occured due to the problems encountered during the preparation of Bevasizumab by filling it into the injector and under the responsibility of the pharmacist who prepared it.

In the USA, if Bevacizumab is preferred over the approved options Ranibizumab or Aflibercept, the official regulation as in the USP <797> guideline requires that all processes should be under control, monitoring and recording.

In addition, all side effects that may develop in a patient despite these measures are requested to be reported to the US health authority.

(41) The following statement was included in the e-mail with the subject "FW: Outlook Therapeutics Announces FDA Acceptance of IND for ONS-5010" sent from NOVARTiS Marketing Access Manager (.....) to NOVARTIS Marketing Access Director (.....) on 03.04.2019:

"Mr. Fatih,

A company called Outlook Therapeutics applied to FDA for an ophthalmic formulation of bevacizumab (Avastin).

The link and details of the news are below.

http://www.globenewswire.com/news- release/2019/04/01/1790614/0/en / Outlook-Therapeutics-Announcements-FDA- Acceptance-of-IND-for-ONS-5010.html"

(42) In the e-mail from NOVARTiS Marketing Access Manager (.....) to NOVARTIS Marketing Access Director (.....) and some NOVARTIS employees on 28.01.2019, titled "FW: TOA announcement, unit comments and other objection documents", the following statement was made:

"Meeting with the SSI

To the meeting held with (.....) (General Health Insurance General Manager), (.....) (SSI Medicines Department Head) and (.....) (SSI Legislation Department Head) after the appointment made on 23.01.2019, TOA Secretary General (.....) (me), representing TOA Central Administrative Board, and (.....), representing TOA Medical Retina Unit, attended. During the meeting, which lasted for one hour and 45 minutes, all aspects of the relevant legislation were discussed. At this meeting, SSI Bureaucrats stated that they did not take any decision on any medical issue without consulting the Ministry of Health, all preparations were recommended to them by a scientific committee consisting of 3 Ophthalmologists established in the Ministry of Health, bevacizumab has no difference in effectiveness and safety with licensed products according to the report from the Ministry of Health, it is already heavily prescribed by ophthalmologists and is widely used in important countries abroad, and even if Altuzan is used for only one patient, the cost to the institution is still half as compared to licensed products. At this point, as TOA representatives, we stated that the information given by the Ministry of Health is not correct, the probability of endophthalmitis, which is one in 7.500-39.000 injections with licensed products, increased to one in 2000, even in bevacizumabs prepared with compounding pharmacy, but it increased to one in 425 in case it is applied in our country under current circumstances, and this is the literature information we received from our units. In addition, we explained the intraocular reactions caused by the silicone particles mixed with the injection material in preparation, the high rate of bevacizumab entering the bloodstream compared to other licensed products, and the risks of thromboembolism, cerebrovascular accident and death."

I.2.1.2. Information Requested in Writing

(43) The statement given by the representative of the undertaking in the response letter which was submitted to the Authority's records with the number 4158 on 05.05.2020 with regard to the information request letter sent to NOVARTIS with the number 5653 on 20.04.2020, is as follows, in brief;

- The amendment made on article 4.2.33 of HIC titled "Principles of Drug Use for Eye Diseases" on 28.12.2018, made the use of the Bevacizumab active ingredient drug, an oncology product that is not licensed for eye diseases, mandatory as the first line treatment within the reimbursement system in the treatment of the following ophthalmology indications,: neovascular AMD, DME, retinal vein occlusion, central retinal vein occlusion and choroidal neovascularization due to pathological myopia.

- NOVARTIS is of the opinion that the said restriction was contrary to the legal regulations, especially to the Constitution, Regulation on Authorization of Medicinal Products for Human Use published in the Official Gazette No.25705 dated 19.01.2005, OLD Guide issued by the Ministry of Health and amended over time, Social Security Institution Regulation on Reimbursement published in the Official Gazette No.29620 dated 10.02.2016, Patient Rights Regulation published in the Official Gazette No. 23420 on 01.08.1998, Medical Deontology Regulation published in the Official Gazette No.10436 on 19.02.1960, and the precedent decisions of the Council of State.

- NOVARTIS is of the opinion that this administrative decision, which has made the off-label use of drugs the mandatory first-line treatment, especially with the regulation made in the reimbursement legislation of the SSI, weakens the regulatory system of the Ministry of Health,

- The aforementioned administrative action is clearly unlawful and has caused

irreparable damage; therefore, NOVARTIS filed an action for annulment before the Council of State on 12.04.2019 for stay of the execution and the cancellation of this administrative act.

- After the initial examination of the case, in addition to the SSI, which was added as a defendant by NOVARTIS in the lawsuit petition, the Ministry of Health was also included in the case as the second defendant by the 10th Chamber of the Council of State and It was reported that the request for stay of execution would be evaluated after the plea of the defendant administrations were presented to the court.

(44) In the response letter of NOVARTİS which was submitted to the records of the Authority on 09.06.2020 with the number 5473 with regard to the information request letter dated 04.06.2020 and numbered 6993, the following was briefly stated regarding the marketing strategy of NOVARTIS;

- All activities carried out in the Turkish market regarding medicinal products for human use were regulated by TMMDA under the Ministry of Health and various industry rules determined by AIFD and other non-governmental organizations and the internal policies and procedures of pharmaceutical companies were taken into account.

- The scope of promotional activities was quite limited and some promotional activities such as sponsorships and meetings were subject to TMMDA's pre-approval.

.....(TRADE SECRET).....

(45) In addition, various questions were asked to NOVARTIS in order to obtain information about medicine for human use used off-label. In summary, the undertaking stated:

- Pursuant to the TMMDA Regulation on Promotional Activities of Medicinal Products for Human Use (Promotion Regulation), the promotion of drugs for healthcare professionals can only be carried out within the scope of the areas of use/SPC and PIL, approved within the framework of the authorization, there are two exceptions[9] to this situation,

- AIFD Good Promotion and Communication Principles (AIFD Principles) provides a detailed guide on how to interpret and implement the off-label promotion prohibition regulated in the Promotion Regulation,

- The rules regarding the promotion of drugs only within the scope of approved indications are also included in NOVARTIS' (.....) and procedures,

- Therefore, in accordance with the Promotion Regulation, AIFD Principles and (.....), NOVARTIS can promote all drugs according to the approved indications, no marketing activities can be carried out for indications for which the drug is not approved,

- The main reasons for this situation are the necessity of authorizing the drugs by considering the risk/benefit profiles according to clinical studies and scientifically proven specific usage areas, and the necessity of limiting any use of drugs outside

[9] These exceptions are i) Promotions to be made at international congresses and information provided by the science service of the authorization holder, upon the written request of the physician/dentist/pharmacist. For related legislation, see Article 6 of Regulation on Promotional Activities of Human and Medicinal Products.

the approved areas under the control of the relevant health authorities in order to ensure patient safety and the quality of medical treatment,

- NOVARTIS has not taken any action to discourage or encourage the off-label use of any drug in the last ten years,

- NOVARTIS filed a lawsuit before the Council of State by exercising its legal right against the SSI legislation, which regulates the compulsory use of *Bevacizumab* in first-line treatment, not against its off-label use.

I.2.2. ROCHE

I.2.2.1. Documents Found during On-Site Inspection

I.2.2.1.1. Documents Regarding Objections Made to Public Institutions

(46) The letter dated 05.11.2018 and numbered 77893119-000-E.191660 sent from TMMDA to ROCHE (Document 8) includes the following statements:

"The intravitreal usage status of the products named "ALTUZAN 400 mg/16 ml Concentrated Infusion Solution" and "Altuzan 100 mg/4 ml Concentrated Infusion Solution", for which you have the licenses, were examined by the "Clinical Assessment Commission of Medicinal Products for Human Use".

Although there is information "ALTUZAN is not suitable for intravitreal use" under the heading "Intravitreal use" in the section 4.4. Special warnings and precautions for use in Summary of Product Characteristics of the product in question, since international institutions and organizations take up-to-date decisions allowing this use, not to cause confusion in clinical practice, restrictive statements regarding the intravitreal use of the product should be removed and the whole SPC/PIL should be rearranged accordingly.

In order to continue the operation of the product, I kindly request you to inform and send us two SmPC and PIL samples for investigation, one of which is a working copy, prepared in a way that includes the specified corrections and that the changes are shown in color, and one of which is a black and white clean copy."

(47) The following statements were included in the letter dated 22.11.2018 and numbered 77893119-000-E.203146 sent from TMMDA to ROCHE (Document 8):

"I kindly request you to inform us and do the needful to fulfill the requirements in our letter regarding the products named "ALTUZAN 400 mg/16 ml Concentrated Infusion Solution" and "Altuzan 100 mg/4 ml Concentrated Infusion Solution" for which you have the license, until 03.12.2018."

(48) The following was stated in the letter titled "Response (Ref. No.: R792) to the Authority's requests about intravitreal use status of ALTUZAN 100 mg/4 ml concentrated infusion solution and ALTUZAN 400 mg/16 ml concentrated infusion solution" sent by ROCHE to the Clinical Assessment Unit of TMMDA Drug Authorization Department on 23.11.2018 (Document 8):

"With your letter concerning our products named Avastin 100 mg/4 ml concentrated infusion solution and Avastin 400 mg/16 ml concentrated infusion solution, for which we have import licenses, removal of the statement "Altuzan is not suitable for intravitreal use." in the SPC Special Use Warnings and Precautions section of our products and the statements restricting the intravitreal use of the products and re-correction of the SPC-PIL documents were requested.

Our product Altuzan was specially developed for intravenous use in oncology indications and has been approved by the authorities in this way. Our product wasn't developed for intravitreal use, no study has been done on its efficacy and safety in intravitreal use, no application has been made to any regulatory authority for intravitreal use and no approval has been obtained.

In addition, Altuzan does not contain any preservatives as it was not developed for intravitreal use. This situation may lead to deterioration of sterility of the product due to the use of small doses for more than one patient and thus local eye infections. Since our product is not approved for intravitreal use anywhere in the world, SPC-PIL documents do not contain the necessary storage and usage warnings for intravitreal use. Safety warnings regarding the adverse effects reported for off-label intravitreal use, including endophthalmitis and intraocular inflammation, some of which can lead to death, are included in the SPC-PIL documents.

Our product is included in the "Off-Label Drugs List That Can Be Used Without Additional Approval of TMMDA" for the treatment of various eye diseases. However, since there is no study conducted through intravitreal use, our product does not have an approved indication. For this reason, removing the statements that restrict intravitreal use from the product information may create the perception of promoting off-label use.

For these reasons, we are of the opinion that the phrase "Altuzan is not suitable for intravitreal use." should not be removed from the product information.

The declaration letter received from our global headquarters, containing more detailed explanations on the subject, is presented in the appendix of this letter."

(49) The following statements were included in the declaration letter to be received from the global center mentioned in the letter above:

"Although we are aware of the off-label use of ALTUZAN in the eye, we have never endorsed or recommended this off-label use due to the known serious adverse events. Therefore, we cannot endorse, promote, recommend or, in any way, support this practice. Considering the potential safety concerns mentioned above, it is important the product labeling continues to inform prescribers that ALTUZAN was not formulated for intravitreal use and therefore this area of use is not approved. Removing this statement could imply that Roche is promoting off-label use, and Roche does not agree with, endorse, or promote the intraocular off-label use of ALTUZAN in the eye."[10]

(50) In the letter (Document 8) dated 18.12.2018 and numbered 77893119-000-E.223431 sent from TMMDA to ROCHE, the following was stated:

"Your objection letter (a) and its appendices regarding the products named "ALTUZAN 400 mg/16 ml Concentrated Infusion Solution" and "Altuzan 100 mg/4 ml Concentrated Infusion Solution" for which you have the license, was examined by the "Clinic Assessment Commission for Medicinal Products for Human Use", I kindly request you to inform us and do the needful regarding the fulfillment of the requirements of our letter (b) within 5 working days."

From these expressions, it is understood that ROCHE's objection was not

[10] The original text of the decision includes a translation of the statements to Turkish.

accepted implicitly by TMMDA.

(51) The following was stated in the letter titled "Response (Ref. No.: R860) to the Authority's requests about intravitreal use status of ALTUZAN 100 mg/4 ml concentrated infusion solution and ALTUZAN 400 mg/16 ml concentrated infusion solution" sent by ROCHE to the Clinical Assessment Unit of TMMDA Drug Authorization Department on 20.12.2018 (Document 8):

a) Your letter dated 22 November 2018 and numbered E.203146

b) Your letter dated 05 November 2018 and numbered E.191660

c) Our letter dated 23 November 2018 and numbered E.332447

d) Your letter dated 18 December 2018 and numbered E.223431

With your letters a) and b) for our products named ALTUZAN100 mg/4 ml concentrated infusion solution and ALTUZAN 400 mg/16 ml concentrated infusion solution, for which we have import licenses, removal of the statement "Altuzan is not suitable for intravitreal use." in the SPC Special Use Warnings and Precautions section of our products and the statements restricting the intravitreal use of the products and re-correction of the SPC-PIL documents were requested; and with our letter c), we submitted our objections and explanations that our product is not suitable for intravitreal use.

With your letter d), we were notified that our objection was not approved and that the requirements in the letters a) and b) are to be fulfilled within 5 working days.

We request extension of time until January 31, 2019, as detailed investigation and preparations on the subject should be continued by our global headquarters."

(52) The e-mail with the subject "Correspondence on Altuzan Intravitreal Usage" sent by ROCHE Pharmaceuticals Unit Regulatory Affairs Specialist (.....) to the ROCHE authorities on 04.01.2019(Document 8/1) includes the following:

"Hello,

As you know, the Ministry requested the removal of the statements restricting the intravitreal use of Altuzan from the Altuzan SPC-PIL documents, and we submitted our objection to this.

In return, the Ministry rejected our objection and demanded that we take action, and we requested extension of time until January 31st for the completion of the global evaluation process. Altuzan has been placed on the reimbursement list for these indications, while we have not yet received a response to our request for time.

You can find the Word document containing correspondence and correspondence history in the attachment,..."

From this e-mail, it is understood that TMMDA tacitly rejected ROCHE's time extension request and *Altuzan*, accordingly, was placed on the reimbursement list for *off-label use* in the aforementioned indications.

(53) In the e-mail "Meeting on the "Mandatory use of off-label products" sent by AIFD Market Access Director (.....) to ALLERGAN undertaking employee (.....), BAYER undertaking employee (.....), NOVARTIS Market Access Director (.....), ROCHE Market Access and Public Relations Director (.....) on 03.01.2019, the following statements were included:

"Hello everyone,

As you know, the "mandatory use of off-label products" became a current issue

with HIC, which was published last week. As AIFD, we would like to organize a meeting with both Market Access and Regulatory directors of our members on the subject in order to work on this issue. Taking advantage of our MA SMC meeting tomorrow, we will meet at the AIFD office at 13:00 with the participation of the Regulatory team after the SMC meeting. Sorry for getting organized at the last minute, I hope it fits in with everyone's schedule. Ms. (.....) will also contact the Regulatory team. ..."

(54) The e-mail sent by ROCHE Health Economics and Market Access Manager (.....) to ROCHE officials on 09.01.2019 was as follows:

"https://www.mdmag.com/medical-news/use-of-bevacizumab-for-amd-resulted-in- savings-of-173b-for-medicare-patients

Best wishes, (…), Ph.D.
Health Economics & Market Access Manager"

(55) On the internet address in the e-mail, there is an article titled "Use of *Bevacizumab for AMD Resulted in Savings of $17.3B for Medicare,Patients"*, which outlines the article titled "*Estimating Medicare and Patient Savings from the use of bevacizumab for the treatment of exudative age-related macular degeneration*", published in the American Journal of Ophthalmology[11]. In the article in question, by making retrospective trend analysis, the savings achieved by using *Bevacizumab* instead of *Ranibizumab* and *Aflibercept* from 2008 to 2015 in the treatment of AMD in the USA were estimated to be 17.3 billion USD. Moreover, it is stated that if the savings achieved with the use of *Bevacizumab* not only in AMD treatments but also in DME and *retinal vein occlusion* treatments were examined and estimated within the scope of the study, it was mentioned that the total amount of savings would exceed 17.3 billion USD.

(56) The e-mail with the subject "Fwd: Off-label-AIFD objection letter-TOA opinion" dated 28.01.2019 sent to ROCHE authorities by ROCHE Director of Regulatory Affairs, Market Access, Pricing and Government Affairs (.....)(Document 8/2) includes the following:

"I share the objection letter of AIFD and the opinion received from TOA.

In this process, as Roche, we submitted our objection to TMMDA last week, in regard to the opinion of the global that it should be objected again."

From this e-mail, it is understood that ROCHE's intent was shaped by the will of the global company, and that the objections were made by the decision of the global.

(57) As seen in the appendices of Document 8/2, ROCHE sent a letter to TOA via AIFD on 23.01.2019 and requested scientific opinion from TOA. This request for opinion letter was as follows:

"Dear. Dr. (.....)

With the Communiqué Regarding the Amendment of Social Security Institution, Health Implementation Communiqué published in the 1st Repeated Official Gazette dated 28.12.2018 and numbered 30639, amendments were made to the sub-clauses

[11] Rosenfeld P. J., M.A. Windsor, W. J. Feuer, S.J.J. The Sun, K.D. Frick, E.A. Swanson, D.. Huang (2018), "Evaluating Medicare And Patient Savings From The Use Of Bevacizumab For The Treatment Of Executive Age-Related Macular Degeneration", Ofthalmology in the American Journal, Vol. 191, p. 135-139.

(4.2.33.A – Principles of use of drugs used in the treatment of neovascular age-related macular degeneration, 4.2.33.B - Principles of drug use in retinal vein occlusion and central retinal vein occlusion, 4.2.33.C - Principles of drug use in the treatment of visual impairment caused by choroidal neovascularization (CNV) due to pathological myopia (PM), 4.2.33.Ç – Principles of use of drugs used in the treatment of visual impairment caused by Diabetic Macular Edema (DME)) of the Article 4.2.33, titled "Principles of drug use in eye diseases", of the Health Implementation Communique.

With the amendment, it was stated that drugs containing the active ingredients of Bevacizumab (off-label use), Ranibizumab, Aflibercept, Dexamethasone, Intravitreal implant and Verteporfin should be administered by ophthalmologists pursuant to the 3-month medical board report, which includes 3 eye diseases specialists in tertiary care institutions and will be covered by Social Security Institution only if they are prescribed in accordance with the rules specified in the relevant article.

The relevant prescribing conditions were established for first-line patients and for patients currently undergoing treatment with drugs used for the authorized indication, except bevacizumab.

With the aforementioned regulation, off-label use of a drug is made mandatory in the firs-line treatment, while there are authorized treatment alternatives. In the same way, if a medication change is required in patients whose treatment continues within the licensed indication, the use of off-label medication is made mandatory, although there are licensed treatment alternatives; it is regulated that no payment will be made if these rules are not complied with.

In addition, the drug containing the currently licensed active substance bevacizumab does not have a licensed dose at the recommended loading dose in HIC 4.2.33.

We request the scientific opinion to be prepared by the Turkish Ophthalmology Association for the assessment of possible risks of the mandatory use of bevacizumab active substance, which is not authorized at the appropriate loading dose and concentration specified in HIC, in related eye diseases, off-label (under the threat of non-refundment) in terms of the patients to whom the treatment will be administered and the physicians who will perform such a treatment, while there are alternative products authorized for the relevant indication within the framework of the information given above.

We kindly request you to take the necessary action.
Kind regards,

(.....) Secretary-General ”

(58) In response to this letter, TOA sent a scientific opinion to AIFD on 26.01.2019. TOA's opinion letter was as follows:

“Dear (.....)

General Secretary of Researcher Pharmaceutical Companies Association

Social Security Institution, with the amendment made in the Health Implementation Communique (HIC) on 28.12.2018, regulated, in Article 25, the use and reimbursement of anti-VEGF treatments such as Bevacizumab (Avastin or Altuzan, Roche), Ranibizumab (Lucentis, Novartis), Aflibercept (Eylea, Bayer) in Ophthalmology in Tertiary Care Institutions. The main feature of the Communiqué is that bevacizumab is the primary treatment for reimbursement and it is mandatory for

the first 3 administration (loading dose) (Article 5). In addition, in cases whose treatment continues with licensed products, switching to bevacizumab is mandatory when switching between these products (Article 4). Apart from this, algorithms are recommended for 4 different conditions, one for each listing the treatment options, (Age-Related Macular Degeneration, Diabetic Macular Edema, Retinal Vein Occlusion and Degenerative Myopia) and it is mentioned that SSI payment will be made in case actions are taken within this plan (Article 4.2.33 -A, B, C and D). In the same communiqué, it is stipulated that bevacizumab should be prepared under sterile conditions in the operating room, who will do this preparation is not specified, and the doctor is left in the sole responsibility in practical terms (Article 4). Finally, Article 45 of the Communiqué states that the implementation concerning Eye Diseases specified in Article 25 will start after 1 month, and accordingly, the implementation will start on January 28, 2019.

As it is known, Ranibizumab (Lucentis, Novartis) and Aflibercept (Eylea, Bayer) are licensed anti-VEGF products that can be used intravitreally in our country. Bevacizumab (Altuzan, Roche), on the other hand, is not a licensed product, and there is the statement "not suitable for intravitreal use" in its package insert. In other words, the potential risks of intraocular use are emphasized beyond being an off-label drug.

In the legislation of the Ministry of Health, the use of off-label drugs is subject to important conditions. For example, in the announcement published by the Vice Presidency of Economic Research and Information Management of TTMDA on 17.05.2013, a clear limitation was introduced with the sentence "While there is an authorized treatment option, off-label drug use is not recommended for patients who can be treated with drugs within the approved indication and standard dose.".

Article 4-(1), which was published later and which contains the General Principles of the TMMDA Off-Label Drug Use Guide and, indicates the same rule as a general basis, with the statement "In our country, the use of off-label drugs is not allowed for diseases that can be treated with drugs within the approved indication. However, if there are treatment options that provide significant advantages in line with scientific data, the request for off-label drug use is evaluated by the Institution."; interestingly, bevacizumab is included in the list of off-label drugs that can be used without the approval of TMMDA in the appendix of the letter. In other words, by including bevacizumab in prescription drugs without the permission of the ministry although there are authorized products, the communiqué has been made contradictory with its own main principles stated at the beginning.

TOA Central Administrative Board received opinions from 3 related units (Medical Retina, Vitreo-Retinal Surgery and Uvea-Behçet Units) on the aforementioned development and according to these assessments, the units, almost completely in agreement, stated that although there are differences between the diseases specified in the communiqué in terms of effectiveness, bevacizumab is an effective product, although not as much as licensed products; the sentence in the communiqué, indicating the conditions where bevacizumab is contraindicated stated in the treatment algorithms, is not clear; since there is no compounding pharmacy in Turkey for dividing the drug, and in order to reach the dose (1.25 mg/0.1 ml, this was later corrected as 1.25 mg/0.05 ml by the institution) specified in the communiqué, the drug needs to be diluted twice after division, this will cause patient and physician risks especially in terms of endophthalmitis risk, it is a safety issue; in terms of functionality, it will further complicate the operating room conditions, which are already heavy in

institutions providing tertiary health care, and create a blockage. Our units also found the articles 4.2.33 -A, B, C and D of the communiqué, which gives treatment algorithms for 4 diseases, extremely contrary to current scientific treatment approaches.

TOA Central Administrative Board submitted petitions to the SSI and the Ministry of Health with the signature of our President, on 25.01.2019, and requested consultation from the Ministry of Health on how our colleagues, who were faced with two different legislations, should act in this process.

…

Prof. Dr. (.....)

the Secretary General of TOA

On Behalf of the Central Administrative Board"

(59) The following statement is included in the e-mail with the subject "Off-label-AIFD objection letter-SSI response" sent to two employees of ALLERGAN, two employees of BAYER, NOVARTIS Regulatory Department Manager (.....), NOVARTIS Market Access Director (.....), ROCHE Market Access and Public Relations Director (.....) by AIFD Health Policy Director (.....) on 28.02.2019 (Document 8):

"Good morning,

We received a response from SSI to our objection letter submitted to SSI about off-label.

You can find the answer letter attached. We immediately started the legal assessment process with its English translation.

It will also be assessed at the Board of Directors meeting to be held tomorrow.

…"

In the response letter attached to this e-mail sent to AIFD by the General Directorate of SSI General Health Insurance with the number 89843079-641.04-E.2891617 on 20.02.2019, it was stated that the regulations of Social Security Institution, Health Implementation Communiqué, which was published in the Official Gazette dated 28.12.2018 and entered into force on 28.01.2019, were made within the framework of the relevant legislation (Document 8).

I.2.2.1.2. Other Documents

(60) The e-mail with the subject "Fwd: Top 10 Products in the Turkish Market" sent on 11.02.2019 from ROCHE Sales Force Effectiveness Analyst (.....) to ROCHE Marketing Director (.....) and Sales Force Activity Implementation Manager (.....) was as follows (Document 8):

"(.....) hello,

You can find hospital and pharmacy breakdowns and sales data of the first 10 products in the Turkish market in the attached file. (between 2014-2018)

…

(.....)SFE Analyst"

(61) In the Excel file attached to this e-mail, it is seen that according to the sales data, in 2018, among the top ten products in Turkey, *Altuzan* is in the (.....) place in the hospital channel, *Lucentis* is in the (.....) place in the pharmacy channel, and *Altuzan* is in the (.....) place when the hospital and pharmacy channels are considered

together.

(62) In the Excel file named "*Lucentis Value Proposition Campaign Plan*" (Document 8), Lucentis' marketing policy, what kind of brand perception it will create, the scope of the value proposition campaign that will be launched in April 2019, what the success metrics of the campaign are, who is in charge of the campaign in what capacity, the contact information of these people, through which channels the target audiences will be reached in marketing activities, what actions will be taken in which periods of 2019, the brand's aims, and the messages it will give to consumers and doctors are included.

I.2.2.2. Information Requested in Writing

(63) In the reply letter (Document-29) sent by ROCHE, and submitted to the records of the Authority on 27.03.2020 with the number 3021, the correspondence of ROCHE with the Ministry of Health regarding the intravitreal use of *Altuzan* was included, and the related articles were summarized as follows:

- Upon the request of the Ministry to remove the statement "*Altuzan is not suitable for intravitreal use*" with the letters dated 05-22 November 2018, ROCHE shared the following letter on 23.11.2018 and objected to the request of the Ministry. The declaration letter on the subject, received from ROCHE's global headquarters, was pointed out:

"Our product called Altuzan was specially developed for intravenous use in oncology indications and has been approved in this way by the authorities. Our product wasn't developed for intravitreal use, no study has been done on its efficacy and safety in intravitreal use, no application has been made to any regulatory authority for intravitreal use and no approval has been obtained.

In addition, Altuzan does not contain any preservatives as it was not developed for intravitreal use. This situation may lead to deterioration of sterility of the product due to the use of small doses for more than one patient and thus local eye infections. Since our product is not approved for intravitreal use anywhere in the world, SPC-PIL documents do not contain the necessary storage and usage warnings for intravitreal use. Safety warnings regarding the adverse effects reported for off-label intravitreal use, including endophthalmitis and intraocular inflammation, some of which can lead to death, are included in the SPC-PIL documents.

Our product is included in the "Off-Label Drugs List That Can Be Used without Additional Approval of TMMDA" for the treatment of various eye diseases. However, since there is no study conducted through intravitreal use, our product does not have an approved indication. For this reason, removing the statements that restrict intravitreal use from the product information may create the perception of promoting off-label use.

For these reasons, we are of the opinion that the phrase "Altuzan is not suitable for intravitreal use" should not be removed from the product information.

The declaration letter received from our global headquarters, containing more detailed explanations on the subject, is presented in the appendix of this letter."

- In the letter dated 18.12.2018, it was stated by the Ministry that ROCHE's objection was not approved, and that the requirements specified in the letters dated 05.11.2018 and 22.11.2018 should be fulfilled within five days. In the letter sent to the Ministry by ROCHE dated 20.12.2018, thereupon, an extension of time until 31.01.2019 was requested since detailed investigations of ROCHE's global

headquarters on the subject continue. This request was accepted with the Ministry letter dated 04.01.2019.

- With the letter dated 23.01.2019, ROCHE again objected to the Ministry's request with the following statements, and another declaration letter was submitted from the ROCHE global headquarters:

“Our product called Altuzan has been specially developed for intravenous use in oncology indications and has been approved in this way by the authorities. Our product was not developed for intravitreal use, no studies have been conducted on its efficacy and safety in intravitreal use, no application has been made to any regulatory authority for intravitreal use and no approval has been obtained.

The statement regarding intravitreal use in our product SPC-PIL documents is dependent on the fact that our product has not been approved by any authority in the world for intravitreal use and there is no relevant efficacy and safety data to support such use. Removing this statement may mislead physicians and patients about the safety of this use, as it would suggest that our company has new efficacy and safety data for intravitreal use.

We would like to explain the practices in force in international authorities regarding the intravitreal use of our product.

FDA product information documents do not contain information regarding the intravitreal use of Altuzan. FDA requested that the "side effects for intravitreal use" section in the product information be removed, since the safety data of an unapproved indication in the product information may be considered as an indirect promotion of an unapproved indication, and this section was removed for this reason. Intravitreal use of Altuzan has not been approved by FDA.

Although the active ingredient "bevacizumab" of our product has been listed in the guide published by NICE for Age-Related Macular Degeneration disease, there is the statement "Bevacizumab has not been approved for this indication in the UK and may be considered as an unapproved drug for this indication by the Medicines and Health Agency (MHRA). This guide may provide information beyond the scope of the UK registration of the product, but is not a recommendation for the use or approval of this product.” Thus, physicians are informed that Altuzan has not been approved for intravitreal use. Since NICE is not a licensing institution, the aforementioned statements in the guide cannot be accepted as an approval for intravitreal use.

EMA product information documents contain the statement "Altuzan is not suitable for intravitreal use." in line with our SPC-PIL documents, since the said use is not approved.

For these reasons, we believe that the statement “Altuzan is not suitable for intravitreal use.” should not be removed from the product information.

The declaration letter received from our global headquarters, containing more detailed explanations on the subject, is attached to this letter.”

- With the Ministry letter dated 01.02.2019, ROCHE's second objection was not accepted and it was reported that the licenses of the products would be suspended if the requirements were not fulfilled within five working days. With the letter dated 05.02.2019, the SPC-PIL documents were submitted for review by ROCHE.

- Finally, with the Ministry letter dated 01.03.2019, since no indications related to ophthalmology were approved, removal of the SPC - Section 4.4 and PIL - Side effects sections and statements about systemic effects/side effects was requested. With the letter dated 15.03.2019, the necessary arrangements were submitted to the

Clinical Assessment Unit and the application was approved on 10.05.2019.

(64) ROCHE's response letter numbered 4155 submitted to Authority's records on 04.05.2020 (Document-44), which was written in response to the information request letter (Document-30) dated 20.04.2020 and numbered 5654, stated that the following issues were pointed out in the regulations made as of 28.12.2018 and the "Announcement About the Regulations Made Regarding the Decisions of the Drug Reimbursement Commission for 2018/1st Term published by SSI on 25.01.2019":

- In terms of intraocular treatments, the existing reports of the patients who are still being treated before the regulation, are valid until the end of their expiry period,
- For patients whose treatment with Ranibizumab or Aflibercept started before 28.01.2019 and who are currently under continuation treatment, it is possible to continue treatment with drugs with these active substances,
- Health committee reports will be issued for the use of drugs with active substance Bevacizumab, Ranibizumab, Aflibercept, Dexamethasone intravitreal implant and Verteporfin for a period of three months initially and for a period of one month for continuation treatment, the criteria in the second and third paragraphs of article 4.2.33. of the HIC will be specified in each report,
- If it is used for more than one patient, it is possible to invoice the entire drug on behalf of the last patient applied on that day, and in cases where the necessary conditions cannot be provided, it is possible to invoice using a single vial of drug for each patient.

(65) In the same letter, it was stated by ROCHE that no judicial action was taken regarding the change made on 28.12.2018 on and came into force on 28.01.2019 on the HIC article 4.2.33. titled "Principles of drug use in eye diseases" and in the sub-clauses of this article.

(66) In summary, in the response letter of ROCHE, , which was submitted to Authority's records on 09.06.2020 and with the number 5474, with regard to the information request letter sent with the number 6994 on 04.06.2020, the following was stated:

.....(TRADE SECRET).....

(67) In the same letter, it is stated that there are seven products in total, including *Pegasys, Cellcept, Mabthera, Actemra, Tamiflu, Roferon, Xeloda,* which are used without approval from the Ministry, except for Altuzan with Bevacizumab active substance, and there are 31 medicinal products for human use used off-label with additional approval.

It is stated that there is no marketing strategy for medicinal products for human use used off-label.

(68) In addition, ROCHE states that it has not taken any initiative in the last 10 years before public institutions and organizations and courts to encourage or discourage the use of its off-label products.

(69) In addition, it is stated that ROCHE has not taken any initiative in the last 10 years before public institutions and organizations and courts to prevent the use of

any off-label drug of its competitors against a licensed medicinal product for human use, and also their rivals has not carried out a similar process against ROCHE's off-label drugs.

(70) In the letter, it is also stated that the SPC/PIL amendment process, which was approved on 30.05.2014, started with ROCHE's application dated 29.12.2011. According to the explanations made in the letter and the attached documents, the development of the process was as follows:

(71) With the letter of ROCHE dated 29.12.2011, changes to Altuzan SPC and PIL information were requested, stating that they would be in line with the original reference documents, it was stated that the reference documents for SPC and PIL were CDS 24.0 (Core Data Sheet Version 24.0) and EU PIL, respectively. According to the request for changes and reference documents;

- In the CDS.24.0 document, which is the reference document of SPC presented in the appendix of the letter,
  - Sections 2.2. and 4.2. state that *Avastin* is not formulated for intravitreal use,
  - In section 2.4.1., there is a brief explanation under the heading “Serious eye infections following unapproved intravitreal use” and
  - In section 2.6.2., the line “Eye diseases (reported in unapproved intravitreal use)” in the table “Adverse reactions reported post-marketing” provides an explanation and some statistics.
- On the other hand, the changes requested by ROCHE to be made in the SPC are as follows:
  - Adding the statement “ALTUZAN is not suitable for intravitreal use.” to article 4.2,
  - Arrangement of clauses 4.4. and 4.8. like the clauses 2.4.1 and 2.6.2. of CDS 24.0,
  - Finally, addition of the statement “ALTUZAN is not formulated for intravitreal use.” to the clause 6.6.

(72) In the EU PIL (with the approval date 24.11.2011), which is stated as the reference document of PIL, side effects that may occur when *Avastin* is injected directly into the eye are listed, except for its approved use in cancer treatment. The requested change in *Altuzan*'s PIL is in line with this.

(73) While there is no statement in the original reference documents that *Altuzan* is not suitable for intravitreal use, it is noteworthy that a statement for this was requested to be added to article 4.2. of the SPC. This finding will be discussed in the assessment section.

(74) On the other hand, following the application dated 29.12.2011, ROCHE's letters dated 24.01.2012 and 29.04.2012 and applications regarding other indications were evaluated within the same process as the application dated 29.12.2011.

I.2.3. BAYER

(75) In the response letter sent by BAYER, dated 08.05.2020 and numbered 4331, the following points were briefly stated:

- It was stated that a negotiation was held between BAYER and NOVARTIS officials on 02.11.2018 in order to assess the administrative and legal steps that can be taken against the HIC change dated 28.12.2018, and after this negotiation, six

meetings were held within AIFD on 09.11.2018, 04.01.2019, 11.01.2019, 18.01.2019, 08.02.2019 and 01.03.2019, respectively. Details of the aforementioned negotiation and meetings are given below:

a. In the negotiation between the Head of BAYER Pharmaceuticals Department (.....) and the General Manager of NOVARTIS Pharmaceuticals (.....) dated 02.11.2018, (.....), stated that he had concerns, although not directly against the off-label use of drugs, because the relevant regulation would limit the freedom of decision of doctors and pose a risk for patients, and the parties decided to share their opinions on the new legal arrangement made, with the participation of the legal advisors of the undertakings within the body of AIFD "*within the framework of the method most appropriate to the law*".

b. In this regard, an information note reminding the competition law rules was shared by the BAYER Legal Counsel (.....) with the relevant BAYER employees at the very beginning of the process, to be taken into account in any possible written or oral interactions to be made with competitors or AIFD officials. (01.11.2018 and 02.11.2018 dated e-mails).

c. Within this scope, a meeting was held on 09.11.2018 with the participation of AIFD, NOVARTIS and BAYER officials and legal counsels to discuss the HIC changes summarized above. In addition to the legal counsels of BAYER and NOVARTIS, AIFD Secretary General (.....), AIFD Assistant Secretary General (.....) and AIFD's competition law counsel also attended the meeting, and before the start of the meeting, sensitive issues with respect to competition law were reminded to the participants by the AIFD competition law counsel. Likewise, BAYER Pharmaceuticals Department Manager (.....) emphasized at the very beginning of the meeting that the purpose of the meeting was not to discuss commercial matters, but only to share views on the new Communiqué. As a matter of fact, in the said meeting, ideas on the possible effects of the new Communiqué and possible actions to be taken against the new Communiqué were exchanged, and it was highlighted that the undertakings could individually file a lawsuit against the new Communiqué. Following the meeting, a meeting note was prepared by the BAYER Legal Counsel (.....) and this meeting note was submitted to the BAYER Market Access Manager (.....) and the BAYER Pharmaceutical Department Manager (.....).

d. It is understood that there was no discussion at the AIFD *"Market Access SMC"* meeting held on 04.01.2019 regarding the regulation to make the use of the off-label product mandatory, which was made with the new Communiqué. As can be seen from the meeting minutes and the relevant presentation, it was decided to assess this issue only at the working group level by the relevant member companies. It is known that (.....) and (.....) from BAYER attended the meeting on the mandatory use of off-label products, which was held in the afternoon of the same day, right after this meeting. The participant list or meeting minutes of the meeting in question were not shared by AIFD. According to the information received from BAYER employees, at the said meeting, HIC changes were discussed in general and it was stated that AIFD should be involved in the process through legal means.

e. Board of Directors meetings were held at AIFD on 11.01.2019, 08.02.2019 and 01.03.2019. However, BAYER did not participate in these meetings as (.....) was not a member of the board of directors on the said dates. However, after the AIFD Board of Directors meeting held on 11.01.2019, a teleconference was held by AIFD. Market Access Manager (.....) attended the meeting on behalf of BAYER. In the said teleconference, the participants were informed that the AIFD had taken a decision to

object to SSI and it was suggested that the objection should be supported by scientific opinions. There is no participant list and note of the teleconference in question.

f. Dr. Viktor GEISLER attended the general managers meeting held in AIFD on 18.01.2019[12]. At this meeting, AIFD stated that they were against the regulation to make the use of off-label products mandatory, that studies were being carried out on legal steps to be taken in this regard, and that a medical/clinical opinion would be requested from TOA and/or a specialist physician on this issue. Following the said meeting, AIFD requested scientific opinion from TOA on 23.01.2019, and TOA submitted its opinion letter dated 26.01.2019 to AIFD in regard with this request.

g. The Market Access Manager (.....) attended the teleconference meeting organized by AIFD after the AIFD Board of Directors meeting held on 01.03.2019, on behalf of BAYER. In the said teleconference, the AIFD official gave information about the decisions taken at the AIFD Board of Directors meeting held on the same day, and it was announced that AIFD would not file a lawsuit against the new Communiqué, but could participate in if a lawsuit was filed by member companies.

h. Finally, two scientific meetings were held by BAYER with the participation of ophthalmology specialists, in Izmir on 12.01.2019 and in Ankara on 13.01.2019, with the aim of assessing the changes brought by the new Communiqué scientifically/medically. The place, date, agenda, list of participants and the presentation text used during the meetings were sent by BAYER.

i. In addition, Bayer held unorganized, one-on-one meetings with SSI officials, some bureaucrats and physicians at various times, with the aim of canceling the new Communiqué.

- It was stated that two separate lawsuits were filed by BAYER against the relevant HIC change and an objection was made to SSI. The details of the mentioned lawsuits and appeals are as follows:

a. On 28.01.2019, an application was made to the SSI to reverse the changes established in the new Communiqué. In addition, applications were made to the Ministry of Health, the Ministry of Treasury and Finance, the Presidency of Strategy and Budget, and the Health and Food Policy Board. SSI rejected the reversion request on 25.01.2019.

b. Following the rejection decision, SSI published the Announcement Regarding the Regulations Made in Intraocular Drug Applications with Regard to the 2018/1st Term Drug Reimbursement Commission Decisions dated 05.03.2019. BAYER filed the lawsuit numbered 2019/4118 E. before the 10th Chamber of the Council of State for the annulment of the SSI process, the Announcement, HIC's articles 4.2.33, 4.2.33.A, 4.2.33.B, 4.2.33.C, 4.2.33.Ç, and SSI's decision dated 18.02.2019. The request for a stay of execution was rejected and the lawsuit continues.

c. A new Communiqué was issued by SSI on 04.09.2019 and a new administrative procedure was established by amending HIC's 4.2.33, 4.2.33.A, 4.2.33.B, 4.2.33.C articles. BAYER filed an action for annulment with a request for stay of execution on 28.09.2019 against this new administrative act. This case continues to be heard before the 10th Chamber of the Council of State with the number 2019/11654 E.

[12] The meeting date, which was 18.01.2019, was inadvertently stated as 19.01.2019 in the meeting minutes.

I.2.4. SANOFI

(76) In the response letter sent by SANOFI, dated 05.05.2020 and numbered 4171, the following was stated in summary:

- Zaltrap, an authorized product of SANOFI, contains the same active substance as Eylea, but is only used in the treatment of metastatic colorectal cancer patients,

- In order to minimize the possibility of medication errors and to facilitate the reporting of side effects and to distinguish the formulation of the drug from Eylea, the FDA (U.S. Food and Drug Administration) requested the addition of "ziv" to the name of the active substance (*ziv-aflibercept*),

- Zaltrap is not used for eye treatments.

I.2.5. ALLERGAN

(77) In the response letter sent by ALLERGAN with the number 4338 on 08.05.2020, it was stated in summary that they did not attend any meeting about the use of *Altuzan* in the treatment of eye diseases, and that the meetings organized or attended by Allergan were related to the areas of use of *Ozurdex* in HIC[13].

(78) When the annexes of the related response letter are examined, it is seen that:

- Ozurdex, an authorized product of Allergan, contains Dexamethasone (intravitreal implant) active substance and is in the S1B ATC-3 class, while Eylea, Lucentis and Visudyne are in the S1P group,

- Ozurdex is not in the group of drugs with anti-VEGF properties such as Lucentis and Eyelea, including Altuzan, and is in the group called corticosteroids,

- In the presentation made at TMMDA on 22.01.2019, Aflibercept, Bevacizumab and Ranibizumab were compared in terms of visual acuity, OCT (optical coherence tomography) results and APTC issues after two years of use, Ozurdex and anti-VEGF drugs had similar response rates to treatment,

- Three anti-VEGF products, Ranibizumab, Bevacizumab, and Aflibercept, were compared with Ozdurex in terms of indications, side effects, and average annual cost per patient,

- It was stated that although the use of Ozurdex is higher in terms of unit costs compared to the use of Altuzan, the annual cost of use is lower.

I.2.6. AIFD

(79) In the response letter sent by AIFD dated 08.05.2020 and numbered 4336, in summary, the following was stated:

- An objection was made to SSI on 19.02.2019 for the abolishment of the HIC change dated 28.12.2018, and in the response to the objection, it was stated that action was taken within the scope of the legislation by taking the opinions of Representatives of the Strategy and Budget Presidency, the Ministry of Treasury and Finance, the Ministry of Health, and academic specialist physicians, about the relevant changes,

- The objection petition sent to SSI was also shared with TMMDA, Presidency of Strategy and Budget, Ministry of Treasury and Finance,

---

[13] When the relevant meeting minutes are examined, it is understood that the meeting agendas cover the assessments of Ozurdex's performance in the market against HIC regulations.

- In the e-mail sent to AIFD on 25.04.2019 by BAYER and NOVARTIS, which filed an action for annulment against the relevant HIC change, the decision taken at the AIFD board meeting dated 01.03.2019 to be involved in these lawsuits was reminded and AIFD was asked to be involved in the process; however, no intervention was requested at this stage considering the fact that it is possible to intervene as long as the lawsuits continue.

(80) The summary table compiled from the information presented about the meetings held at AIFD regarding the use of *Altuzan* in the treatment of various eye diseases is given below.

Table 2- Meetings Held by AIFD

Date	Place/Subject	Agenda	Participant	The Issues Discussed
09.11.2018	AIFD ISTANBUL OFFICE	Oral meeting	AIFD Bayer Novartis	-The news about the change in legislation was received and that the issue could come to the agenda of AIFD in case the change was made.
04.01.2019	AIFD ISTANBUL OFFICE	-Market Access Meeting -Application Of off-label use as primary-care in HIC	AIFD Roche Allergan Bayer Novartis	-Parties were informed about the change, It was decided that -Scientific research of the application of off-label use as primary-care be done, -Assessment of safety risks for patients be made, -Investigation of applications in other countries be examined.
11.01.2019	-AIFD Board of Management meeting -A teleconference was also arranged on the same day.	Application of off-label use as primary-care in HIC	Nine undertakings participated. Novartis and AIFD are among them.	The following decisions were taken: -A medical/clinical assessment from TOA or a related expert would be requested, -The issue would be mentioned at the meeting to be held with TMMDA, -AIFD would object to the use of off-label use as primary-care treatment, -The petition would be shared with TMMDA.
18.01.2019	Ordinary AIFD general managers meeting	Current information on the application of off-label use as primary-care in HIC	16 undertakings participated. Roche, Bayer, and Allergan are among them.	-The SSI regulation regarding the implementation of off-label use as primary-care cannot be accepted, -AIFD should seek opinions from lawyers for possible annulment action and from TOA for medical assessment. As a result of this decision, scientific opinion was requested from TOA on 23.01.2019.

08.02.2019	AIFD Board of Management meeting	-Draft Authorizing Regulation -Off-label drug use	12 undertakings participated. Novartis And Roche are among them	-The opinion received from TOA and the framework of the AIFD legal objection were discussed, -It was decided that the framework of the AIFD objection will be handled within the scope of regulation and patient rights,
				-An appeal was made to SSI and it was decided to share the petition with the Health Services Pricing Commission.
01.03.2019	AIFD Board of Management meeting	-	12 undertakings participated. Novartis and AIFD are among them.	Since the relevant member companies did not have a clear decision, it was decided that AIFD would not file an action for annulment, but could only be involved in the lawsuits filed by the member companies.
5.4.2019	AIFD Board of Management meeting	-	11 undertakings participated. AIFD and Novartis are among them.	It was learned that one member of AIFD filed an action for annulment, and another member would file an action for annulment. Reminding that AIFD should be involved in such lawsuits as per the decision on 01.03.2019, it was decided that this situation would be standard practice. It was decided a decision was taken to obtain information about the legal procedure and costs in order for AIFD to be involved.
Source: Response letter from AIFD				

I.2.7. TOA

(81) In the response letter sent by TOA with the number 4123 on 04.05.2020, in summary, the following was stated:

- They did not hold any meeting on the use of Altuzan or Lucentis, nor did they participate in an organized meeting,

- First of all, a petition was sent to SSI and TMMDA on 25.01.2019 for the removal of the change made on HIC on 28.12.2018, after the relevant petitions were not answered, a lawsuit was filed on 08.04.2019 for the stay of the execution of the action; however, upon the rejection of this request by the Council of State, the decision was appealed before the Board of the Administrative Law Chambers (IDDK), IDDK has not made a decision yet,

- While the lawsuit process was ongoing, endophthalmitis (intraocular infection) developed during the use of Altuzan in the eyes of approximately 20 patients on 17.01.2020 at the Kırıkkale University Medical Faculty Hospital, Ophthalmology Polyclinic.

- The basic principle in OLD Guide was "In our country, the use of off-label drugs for diseases that can be treated with drugs within the approved indication is not allowed"; however, it was updated with the amendment[14] made on 08.02.2019, thus the contrariness of the HIC regulation to the Guideline was resolved.

(82) The examples given regarding the off-label use of *Altuzan* in the treatment of various eye diseases are as follows:

- Avastin is used in the USA, Israel, England and Italy by dividing/making it divided under the authority and responsibility of the central health authority and on the condition that it is delivered to the physician under appropriate conditions in order to minimize Altuzan's risk of infection, but in our country, the responsibility of dividing is left to doctors,

- As stated in the fourth paragraph of HIC 4.2.33., Bevacizumab administration should be performed under sterile conditions in operating room conditions,

- Issues such as by whom and how the dividing would be carried out in the operating room, who would be responsible for the dividing under sterile conditions, whether the rest of the drug would be used, and whether the storage conditions would be sufficient are completely unclear,

- In the US, Avastin is widely used because the Supreme Court issued a case law legalizing the use of unlicensed drugs, Bevacizumab is supplied pre-filled and labeled for use in each patient, there are official regulations that all processes from preparation of the drug for the injector to the patient should be under control, follow-up and recording,

- In Israel, England and Italy, the process of dividing the drug from the original size bottle, packaging, adjusting the dose and performing these processes in the necessary sterile conditions and in the cold chain environment required to maintain the effectiveness of the drug are left to the pharmacies authorized and followed by the administration, in this way, physicians and patients have the opportunity to reach the drug in the safest possible way and the risk of infection that may arise from the application is minimized.

I.2.8. IQVIA

(83) In the response letter sent by IQVIA with the number 4163 on 05.05.2020, annual and monthly sales information of Lucentus, *Eylea* and *Altuzan* since 2016 are provided. According to the EMPHRA (European Pharmaceutical Market Research Association) classification on which the Commission and the Institution base its examinations, there are products named *Eylea*, Lucentus and Visudyne in the S01P ATC-3 group. However, since it does not include indication breakdown, it is not possible to understand how much of *Altuzan*'s sales are due to the use in these treatments using the sales data of IQVIA, and it is not possible to calculate the shares in the relevant market.

(84) According to the data provided by IQVIA, 95-99% of the sales of the three products in the S01P ATC-3 group are made to the community pharmacy channel. On the other hand, when the monthly sales since January 2016 are analyzed to see

[14] ARTICLE 4 - "(1) For diseases that can be treated with drugs within the approved indication in our country, off-label drug use is assessed by the Institution only if there are treatment options that provide a significant advantage in line with scientific data. In addition, the use of the drugs included in the "Off-Label Drugs List That Can Be Used Without Additional Approval of TMMDA" in the indications included in this list has been approved by the Authority, and there is no need to apply to the Institution for the request for the use of off-label drugs on patient basis.

how the sales of the related products have been affected by the HIC change dated 28.12.2018, the following points are inferred:

- There has been a significant decrease in Lucentis Vial sales since the said period,
- The sales of the Prefilled form of Lucentis started in February 2019, so it is not possible to assess meaningfully how the sales of this product were affected by the HIC change,
- Eylea sales have decreased since February 2019, although there have been fluctuations afterwards, the sales trend have never approached the previous period,
- Visudyne's sales are both very fluctuating and at very low levels compared to sales of other products,
- The sales of the 100 mg form of Altuzan used in intraocular treatments increased significantly in 2019, when the HIC change came into effect.

I.2.9. HOSPITALS

I.2.9.1. (.....)

In the response letter from (.....), the following was stated in summary:

- Zaltrap, an anti-VEGF drug like Lucentis, Altuzan and Eylea, is not currently used in the treatment of eye diseases because of the risk of developing intraocular toxicity, but studies in this area are ongoing,
- Before the HIC change, Lucentis, Eylea and Ozurdex were mainly used for macular edema due to DME and RVT, and Lucentis and Eylea were mainly used for neovascular AMD and CNV due to PM; Altuzan, on the other hand, was preferred in diseases that require anti-VEGF medication by filling out an off-label form and in some rare cases.
- After the HIC change, as the hospital mainly serves patients with SSI insurance, the drug preference is changed and Altuzan is used for the first three months in the treatment of the above-mentioned diseases, if there is no response to treatment after three or five injections, patients switch to other drugs,
- Patients obtain Lucentis, Eylea or Ozurdex from pharmacies, and it is found in studies that the rate of endophthalmitis in these drugs, which are in the form of pre-prepared vials or implants for use in the treatment of only a single patient, is low, as 1 in 7500 to 39000 injections,
- On the other hand, during the use of Altuzan, which can be obtained from pharmacies by the patient if it cannot be found in the hospital pharmacy, the rate of endophthalmitis is high, as 1 in 425 injections, because the drug is administered to more than one patient from a single vial in divided doses,
- The reason for the high risk of endophthalmitis in Altuzan is that 1 box of the drug is sent from the hospital pharmacy every day and 1.25 mg is filled from Altuzan 100 mg/4 ml vial by the ophthalmologist into a 0.05 ml injector and the specified dose is administered to more than one patient.
- Obliging the use of Altuzan as mandatory primary-care by SSI makes off-label use of a drug routine and may result in physician malpractice,
- There has not been a case of malpractice among hospital physicians yet, but it is thought that this situation is likely to occur if Altuzan continues to be used, it is predicted that a situation similar to the situation experienced in Kırıkkale University may also be experienced in (.....).

- This situation was reported to the Ministry of Health and SSI by TOA, but no changes were made by the competent authorities in the use of Altuzan,

- It was also stated by TOA that Altuzan should be divided into doses, packaged and distributed in this way by providing the necessary hygiene standards in drug production centers.

I.2.9.2. (.....)

(85) In the response letter from (.....), the following was stated in summary:

- *Zaltrap*, which contains the active substance called Ziv-aflibercept, is not authorized for the eye, but this drug can be used off-label in the treatment of eye diseases,

- In some diseases (for example AMD), only anti-VEGF molecules are used, while intravitreal dexamethasone implant is used in the treatment of diabetic macular edema and vein occlusion in addition to those,

- No significant change was observed in the use of eye medications before and after the HIC change dated 28.12.2018; in the treatment of the aforementioned diseases, the percentage of use according to the active substance is (.....) for *Aflibercept*, (.....) for *Ranibizumab* and (.....) for *Dexamethasone* implant,

- Since Becavizumab does not have an ophthalmology license, *Altuzan* is not preferred even after the HIC change,

- Patients obtain their medicines from private pharmacies themselves,

- It has been heard that physicians have faced medical malpractice lawsuits as a result of the use of *Altuzan*, and the infection cases in Kırıkkale University Faculty of Medicine are concrete examples of this,

- Because *Altuzan* is used off-label, physicians have serious concerns about using *Altuzan*.

I.2.9.3. (.....)

(86) In the response letter from (.....) HOSPITAL, the following was stated in summary:

- *Lucentis* and *Eylea* are used in the treatment of choroidal neovascularization in AMD and pathological myopia, macular edema due to diabetes or macular edema due to retinal vascular occlusion, *Ozurdex* is used in the treatment of macular edema due to branch retinal vein occlusion or central retinal artery occlusion, non-infectious veitis, and *Altuzan*, which is produced for metastatic colon cancer, is used in cases where licensed drugs cannot be used in the indications of *Lucentis* and *Eylea*,

- After the HIC change on 28.12.2018, patients were required to take at least three doses of *Altuzan*, but if the patient pays for himself, treatment can be started with drugs other than *Altuzan*,

- Prior to the HIC change mentioned in the (.....), licensed anti-VEGF agents were used in the relevant treatments at the following rates: (.....)% *Lucentis*, (.....)% *Eylea*, (.....)% *Altuzan*, and (.....)% *Ozurdex*; after the HIC change, three doses of *Altuzan* are applied as the primary-care in the related treatments, and then the drugs licensed for anti-VEGF are switched according to the clinical condition of the patient,

- The usage methods and application doses of the mentioned drugs do not change depending on the stages or types of the diseases, but the frequency of application may vary,

- *Lucentis*, *Eylea* and *Ozurdex* boxes are used in a single patient and applied under appropriate sterilization conditions, and *Altuzan* is divided into 5-10 doses under sterile conditions according to the number of patients per day,

- Ophthalmologists working at (.....) heard that lawsuits were filed due to medical malpractice due to the use of *Altuzan* in different hospitals, and they are concerned about the risk of infection caused by the application of *Altuzan* in doses.

I.2.9.4. (.....)

(87) In the response letter from (.....), the following was stated in summary:

- The usage patterns of the aforementioned drugs and the dosage and frequency of administration are similar in related treatments; *Altuzan* has a usage rate of (.....)% and the other drugs have a (.....)% usage rate; however, these rates changed to approximately (.....)% *Altuzan* and (.....)% *Eylea* and negligible amounts of *Lucentis* in 2020,

- The aforementioned drugs can only be prescribed from public hospitals, but can be supplied by private hospitals,

- No medical malpractice lawsuit has been filed against any doctor in the hospital against the use of *Altuzan*, but the risks of infection arising from the use of *Altuzan* may cause concern for physicians.

I.2.9.5. (.....)

(88) In the response letter from (.....), the following was stated in summary:

- There was no significant change in the use of eye medications in the hospital before and after the HIC change dated 28.12.2018; (.....)% *Altuzan*, (.....)% *Eylea*, (.....)% *Lucentis*, and (.....)% *Ozurdex* are used in related treatments, and the usage methods, application doses and frequencies of the aforementioned drugs are similar,

- No medical malpractice lawsuit was filed against the doctors working in the hospital regarding the use of *Altuzan*.

I.2.9.6. (.....)

In the response letter from (.....), the following was stated in summary:

- Before and after the HIC change dated 28.12.2018, (.....) *Lucentis* and *Eylea* were used, no off-label drugs were used in the hospital, and therefore, there was no dose sharing among the patients,

- Although SSI prioritizes the use of *Altuzan* with the HIC change, physicians have concerns on this issue due to the presence of two different drugs that are indicated in the relevant treatment areas, lawsuits arising from medical practice errors and legal regulations,

- The use of a vial of *Altuzan* by dividing it in unsuitable conditions creates a risk of serious infection (endophthalmitis), as a result of the application of *Altuzan* by dividing it to 30 patients in Kırıkkale, endophthalmitis occurred in 17 patients and vision loss of various degrees occurred in almost all of them,

- In the USA, *Altuzan* is widely used in eye treatments, while there are pharmacies abroad that will divide this drug into doses under sterile conditions (*compounding pharmacies*), there are no such pharmacies in Turkey, so ophthalmologists refrain from using this drug.

I.2.9.7. (.....)

(89) In the response letter from (.....), the following was stated in summary:

- *Zaltrap* is also among the drugs used in the treatment of related eye diseases on a global scale, but this drug is not authorized for use in eye treatments in Turkey,

- In diseases that require intraocular injection, a loading dose is applied once every month for the first three months, then, generally, a total of 7-9 doses of the drug should be administered in the first year, and 4-5 doses in the second year, depending on the course of the disease; although these dose intervals may vary depending on the course of the disease, the interval between two dosing should be at least one month,

- Before the HIC change dated 28.12.2018, in (.....), *Eylea* was used at (.....)%, *Lucentis* was used at (.....)%, and *Altuzan* was never used,

- After the HIC change, the first three doses of treatment started to be applied with *Bevacizumab* by explaining to the patients that drugs containing *Bevacizumab* do not have an indication for intraocular use, but these drugs are within the scope of reimbursement, patients who want to start and continue the treatment with drugs with an indication for intraocular use are informed that the application can be made at their own expense,

- Before the HIC change, the patients bought *Altuzan* jointly with other patients and had it applied, since it was more affordable in some centers in our country,

- All over the world and in our country, it has been demonstrated by publications and clinical experience that *Bevacizumab* is as effective as other drugs with indications for intraocular use, it has also been proven that the risk of intraocular infection increases, especially when a vial is distributed to many patients, with a later change in HIC, it is allowed to use one vial for each patient in cases where it is thought that there may be an infection while sharing the vial,

- The *Bevacizumab* report issued for the first three months loading dose to the patients is valid for three months; when the report is prepared, patients can obtain *Altuzan* from the hospital pharmacy or, if this drug is not available in the hospital, the hospital authorities can obtain it from public pharmacies after the "not available in the hospital" stamp is printed on the report; if the patient benefits from *Bevacizumab* after the first three months, the same report procedure is continued; if the physician considers that the patient does not benefit from *Bevacizumab* (criterion = macular thickness is more than 250 microns or there is no increase or decrease in visual acuity), the patient can switch to other drugs,

- Altuzan, which is not prepared for use in the eye, does not have an indication for intraocular use, and is used systemically in the treatment of cancer, is not considered appropriate due to the risk of both toxicity and intraocular infection, the cases of infection due to the use of *Altuzan* in Kırıkkale University Faculty of Medicine also support the aforementioned concern.

I.2.9.8. (.....)

In the response letter from (.....), the following was stated in summary:

- Before the HIC change dated 28.12.2018, (.....)% *Lucentis*, (.....)% *Eylea* and (.....)% *Ozurdex* were used in the hospital,

- According to the HIC change, the first three loading doses of the patients should be administered with *Altuzan*; after three doses of *Altuzan*, the patient can continue the treatment with *Altuzan* or switch to *Lucentis* or *Eylea* by changing the

medication, depending on the patient's response; (.....)% *Lucentis* and (.....)% *Eylea* are used in cases where drug changes are made after the mandatory administration of *Altuzan* in the first three doses,

- *Lucentis* is in a pre-filled injector and can be injected directly into the patient's eye, *Eylea* is in a vial to be the appropriate dose for a patient and can be applied to the patient by being filled into its own injector on the sterile table in the operating room, *Ozurdex* is packaged with a injector system ready for implantation into the eye; on the other hand, *Altuzan* is packaged as 400 mg/16 ml or 100 mg/4 mL IV concentrated infusion solution, 100 mg 16 ml vial usually comes to the hospital, 0.5 ml of the drug from the same vial for each patient should be filled into the injector and administered to the patients, and there is enough dose for at least 6-7 patients in a vial,

- Although the division of *Altuzan* into doses is done in the operating room, the filling of the drug from the vial into injector increases the risk of contamination for each patient, medical malpractice lawsuits will be inevitable after such applications, and therefore, doctors have concerns about the use of *Altuzan*; if it is possible to present *Altuzan* in a sterile injector that can be administered to a single patient, like other drugs, such concerns can be avoided.

I.2.9.9. (.....)

In the response letter from (.....), the following was stated in summary:

- *Lucentis*, *Altuzan*, *Eylea, Zaltrap* and *Ozurdex* are generally used in the treatment of edema and neovascular age-related degenerations related to macular diseases,

- The aforementioned drugs are frequently used in AMD, macular edema due to diabetes, macular edema due to central retinal vein occlusion or branch retinal vein occlusion, and macular edema due to uveitic diseases, in such diseases of the macula, it is often necessary to use the drugs mentioned repeatedly,

- In the period before the HIC change dated 28.12.2018, the usage rates of the aforementioned drugs in (.....) were (.....)% *Altuzan*, (.....)% *Eylea*, (.....)% *Lucentis* and (.....)% *Ozurdex*; after the HIC change, the ranking did not change, but *Altuzan* usage rates approached (.....)%, while the usage rates for *Eylea*, *Lucentis* and *Ozurdex* decreased to (.....)%, (.....)% and (.....)%, respectively,

- *Altuzan* is obtained from the hospital pharmacy and the division into doses is done in the place where the injection will be made to the patient and just before the injection; there is no need for division in the drugs named *Lucentis*, *Eylea* and *Ozurdex*, and the patient obtains these drugs from outside pharmacies with a report,

- They heard that there are cases of malpractice related to the use of *Altuzan*, physicians believe in the efficacy of *Altuzan* but are concerned that the use of *Altuzan* may constitute a medical malpractice, medical sales representatives imply to physicians that the use of this drug may cause medical malpractice, based on the fact that there is no indication that it can be used in the eye in the *Altuzan* package insert.

I.2.9.10. (.....)

In the response letter from (.....), the following was stated in summary:

- Owing to their vascular endothelial growth factor inhibitory effects, in order of frequency, *Lucentis*, *Altuzan*, *Eylea* and *Zaltrap* can be used as intraocular injections for AMD, diabetic macular edema, macular edema due to retinal vein occlusions, cystoid macular edema, macular edema due to myopic choroidal neovascularization,

retinopathy of prematurity, and other retinal diseases that may cause choroidal neovascularization,

- Since *Lucentis* and *Eylea* are produced for direct intraocular injection, the vial doses can be used for one eye of a patient; on the other hand, *Altuzan* and *Zaltrap* are drugs produced for metastatic cancer diseases and authorized for intravenous administration; however, they are used more frequently than intraocular drugs worldwide,

- Due to the fact that *Altuzan* and *Zaltrap* are produced for systemic use, the amount of drug in the vial is high, so the cost of the drug can be reduced by applying it to more patients,

- *Ozurdex*, on the other hand, is an anti-inflammatory, steroidal drug and is used in diabetic macular edema, macular edema due to retinal vein occlusions, cystoid macular edema and macular edema secondary to uveitis, in order of frequency,

- In the treatment of the said eye diseases, the name of the molecule is included in the reports written to the patients, the patient can choose between the drugs containing the prescribed molecule; however, there are currently no different drugs containing the same molecule, all of the mentioned drugs contain separate molecules, but their mechanism of action is similar,

- Depending on the stages or types of the diseases, the use of the said drugs and the application dose may vary only in retinopathy of prematurity, and the application dose is the same in other diseases,

- The number of applications on a monthly basis changes according to the severity of the disease, its continuity and the drug used; *Lucentis* and *Altuzan* are applied once a month, while *Eylea* is applied every two months after the first three doses, and *Ozurdex* is applied every three months,

- Before the HIC change dated 28.12.2018, the frequency of use of drugs used for intraocular injection in (.....) was (.....)% *Lucentis*, (.....)% *Eylea*, and (.....)% *Ozurdex*,

- After the HIC change, the frequency of use of drugs in (.....) is (.....)% *Altuzan*, (.....)% *Lucentis*, (.....)% *Eylea*, (.....)% *Ozurdex*,

- After the drug report is written, *Altuzan* can only be obtained from the hospital pharmacy, and if it is not available in the hospital pharmacy, it is prescribed externally with the approval of the chief physician,

- The smallest vial of *Altuzan* contains 4 ml of drug, and the fixed dose used during intraocular injection is 0.1 ml, since this drug is also used in some cancer diseases in the hospital, it is generally used by sharing the dose in order not to disrupt the treatment of cancer patients, dose sharing is done more often in the chemotherapy units of pharmacies or in the operating rooms in a sterile manner at the bedside due to the insufficient capacity of the chemotherapy units,

- As *Lucentis*, *Eylea* and *Ozurdex* are produced for direct intraocular injection, they contain only enough doses for one patient and there is no need for dose sharing in their use, these drugs can be obtained from pharmacies which patients themselves prefer, with an external prescription after the report is written,

- Physicians may be concerned about the risk of infection due to the need for dose sharing in the use of *Altuzan*.

I.2.9.11. (.....)

In the response letter from (.....), the following was stated in summary:

- *Zaltrap* is not a drug used in the treatment of eye diseases in *(.....)*, Anti-VEGF (containing vascular endothelial growth inhibitory factor) group drugs such as *Lucentis*, *Altuzan*, *Eylea* are used in cases of diabetic macular edema (fluid accumulation in the visual cortex due to diabetes), AMD and edema in the visual cortex due to retinal vein occlusions, choroidal neovascular membrane (deterioration in the visual cortex) due to myopia, *Altuzan* is used off-label in rare cases with similar pathology, *Ozurdex* is used in diabetic macular edema, edema due to retinal vein occlusions and uveitis (intraocular non-microbial inflammatory condition),

- Drugs used in the aforementioned diseases are prescribed to patients as active substanced, the active ingredients of all the drugs mentioned are different from each other; therefore, the patient does not have a chance to choose between drugs with the same active ingredient; however, among the related drugs, *Lucentis*, *Eylea* and *Ozurdex* are sold as single-use preparations, *Altuzan*, on the other hand, does not have a preparation ready for intraocular injection, and it can be administered to more than one patient by dividing the doses from the vials on the market in an appropriate environment; since *Altuzan* should be used in the primary-care, the patient is informed that this drug will be divided into doses, patients who do not want the drug to be divided into doses can continue the treatment with drugs sold as single-use preparations, by their own means; since it will be mandatory to purchase *Altuzan* after the drug is prescribed, the patient can choose the molecule only after the physician informs him/her before the drug is written on the report,

- Before the HIC change dated 28.12.2018, the rate of use of drugs was (.....)% *Altuzan*, (.....)% *Lucentis*, (.....)% *Eylea*, (.....)% *Ozurdex*; after the HIC change, the usage rates of the aforementioned drugs became (.....)% *Altuzan*,(.....)% *Lucentis*, (.....)% *Eylea* and (.....)% *Ozurdex*,

- Drugs such as *Lucentis*, *Eylea* and *Ozurdex*, which can be administered without need to be divided into doses for the patient, are brought to the hospital after being prescribed to the patient from the pharmacy chosen by the patient on the day of injection, and Altuzan is obtained from the institution's pharmacy after being prescribed to the patient and divided into doses in operating rooms,

- Although the physician is allowed to take initiative and administer a single vial of *Altuzan* to a patient and discard the remaining doses, pursuant to HIC, the physicians are informed that this may cause problems in cancer patients' access to *Altuzan*, thus, if *Altuzan* is to be used in the eye, it is divided into doses so that the drug is not wasted,

- No medical malpractice lawsuit has been filed against any physician in (.....) regarding the use of *Altuzan*, but complaints regarding the use of *Altuzan* have been received by the hospital through SABİM (The Communication Center of the Ministry of Health) and CIMER (The Communication Center of the Presidency of the Republic); for this reason, physicians are concerned about the use of *Altuzan*. These concerns stem from two issues, first is that the drug is used off-label and there is no indication for intraocular administration in the package insert, and the second is that the division of the drug into doses poses infection risks,

- Serial endophthalmitis cases were seen after the *Altuzan* application in Kırıkkale, the lawyers consulted by the physicians stated that the change in HIC does not protect the physicians against malpractice lawsuits and the risks for the physicians continue; in addition, due to the fact that an ophthalmologist was ordered to pay approximately 400,000 TL in compensation in the lawsuit filed against him/her after

the *Altuzan* injection, the concerns of the physicians about the use of *Altuzan* increased.

I.2.10. SSI

(90) In the letter of SSI, saved in the Registry of the Authority on 22.05.2020 with the number 4789, the information on the amount and cost of *Ranimizumab*, *Aflibercept* and *Dexamethasone* (intravitreal implant) usage in 2015 and 2016 was presented as follows:

Table 3- Usage Amount and Cost of Ranibizumab, Aflibercept and Dexamethasone within the Scope of Reimbursement

	2015	2015	2016	
	Piece	TL	Piece	TL
Ranibizumab	(.....)	(.....)	(.....)	(.....)
Aflibercept	(.....)	(.....)	(.....)	(.....)
Deksamethasone	(.....)	(.....)	(.....)	(.....)
Source: SSI's Response Letter				

(91) According to the table, it was understood that the total of drugs with *Ranibizumab* and *Aflibercept* active substances was (.....) in 2015 and (.....) in 2016. In the information obtained from SSI, the following were stated regarding the *Altuzan* product:

- The product is currently used as the drug of choice and the recommended dose is 1.25 mg/0.05 ml once every 4-6 weeks,
- It is considered that it would be appropriate to include the drug, which was found to be used in intraocular applications in foreign publications, in the scope of application, in order to make a positive contribution to the public budget, taking OLDL into account,
- The product contains 100 mg and 400 mg, 80 doses can be obtained from the 100 mg/4 ml vial, and it is possible to administer to at least 60 patients, considering the amount of waste that may occur during filling,
- The cost for a single application is (.....)TL for *Bevacizumab* (if applied to 60 patients), (.....)TL for *Ranibizumab*, (.....)TL for *Aflibercept*, and (.....)TL for *Dexamethasone*,
- It is necessary to take certain protective measures in order to prevent healthcare personnel from being at risk during the preparation of cancer drugs, and the drugs in question are also included in this scope; within the measures taken, the single use amount of the drug is applied for each patient, the drug that is not used during the day is discarded, and even if a vial is administered to a single patient, *Altuzan* shows a significant cost advantage with (.....)TL (or *Eylea* with (.....)TL) compared to other drugs,
- On the other hand, there are complaints about the payment of a patient share for each drug supply since intraocular drug applications are considered outpatient treatment and these drugs are not within the scope of exemption,
- Accordingly, regulation was made so that *Altuzan* should be used in AMD,

retinal vein occlusion and DME indications, that the intravenous *Eylea* preparation should be used in the same way, and that no patient shares should be charged for these products.

(92) It is stated that for the patients to be treated for the first time within this scope, treatment with *Bevacizumab* (*Altuzan*) or *Aflibercept* (*Eylea*) active substance will definitely be started, and if it is confirmed that the drug does not provide sufficient effect at the assessment made after three months of application, which is the loading dose, it is possible to switch to other active substances. The opinions of the Ministry of Health regarding the subject were requested by stating that for patients who are still on treatment with other drugs, the necessary criteria that should be included in the health board report should be provided with respect to switching to a drug with Bevacizumab active substance in case of a need for a drug change, and in terms of continuation applying the drug in the same way as in patients who will start the drug for the first time, and especially determining the initiation and change of drug with clear criteria. Upon the opinion, necessary arrangements were made in the Health Implementation Communiqué and it was published in the Official Gazette dated 28.12.2018 and numbered 30639.

(93) SSI examined the data in the MEDULA System on 21.01.2020 and found that *Altuzan* was applied intraocularly in 58 provinces. When the years 2018-2019 were compared, it was found that the number of patients using *Eylea* and *Lucentis* decreased by (.....)% and (.....)%, respectively, while the number of patients treated with *Altuzan* increased by (.....)%, and that the amounts paid for the use of *Eylea* and *Lucentis* decreased by (.....)% and (.....)%, respectively, while the amount paid for the patients using Altuzan increased by (.....)%. As a result of this, it was observed that there was a 22.4% decrease in the relevant public expenditures in 2019.

(94) Scientific publications have shown that the side effects of intraocular drug applications are valid for all three drugs (*Altuzan*, *Lucentis* and *Eylea*), and it is concluded that there is no statistically significant difference between the efficacy of these drugs in large-participant randomized controlled clinical studies and meta-analysis studies.

(95) In the study conducted by the SSI on more than 15,000 patients, it was not found that *Altuzan*, one of the anti-VEGF agents used in the same diagnoses, with similar efficacy and side effects, adversely affected the patient's health. It has been stated that no concrete document has been submitted to the SSI regarding the issue.

(96) When the annexes of the SSI letter are examined, it is understood that the HIC amendment process dated 28.12.2018 went as follows:

- There was intense correspondence between SSI and TMMDA before and after the HIC change. With the letter of SSI dated 06.04.2018, the opinion of TMMDA was requested regarding the change of HIC article 4.2.33. in terms of intraocular drug administration and the use of *Bevacizumab*, which has a much lower cost than other active substances, in related treatments.

- In the response of TMMDA dated 30.07.2018, it was stated that additions were made to the off-label use of *Bevacizumab* in OLDL, effective from 28.02.2018, that all randomized clinical studies comparing this active substance with *Ranibizumab* and *Aflibercept* showed that there is no significant difference in efficacy between them and that the rates of side effects are similar, that starting the related treatments with *Bevacizumab* can be recommended in Turkey as in some countries, and also, again with reference to country examples, in Turkey, the drug can be divided into single-use

units in sterile conditions in centers, and packaged, thus, one vial can be administered to 60 patients; alternatively, it will be appropriate to open the drug in sterile operating rooms and apply it to the patients that day and discard the remaining portion at the end of the day.

- It is understood that in the period after the HIC change, TMMDA submitted an opinion to the SSI with the letters dated 15.02.2019, 21.11.2019, 15.01.2020.

- In the letter sent by TMMDA to SSI dated 15.02.2019, the following explanations were made: the treatment can be continued with the same drugs in patients who have responded with *Ranibizumab* and *Aflibercept*, *Bevacizumab* can be administered as one vial to each patient, and it is possible to use it for other patients; however, it is obligatory to dispose of the unused part on the same day, and vascular pathologies such as myocardial infarction and cerebrovascular accident in the last three months were cases in which all anti-VEGF drugs are contraindicated, and adjustments to be made was required.

- In the announcement of SSI dated 05.03.2019, explanations were made taking into account the TMMDA letter dated 15.02.2019 to be considered with the change made in article 4.2.33. of HIC.

- The changes made to article 4.2.33 of the HIC and especially the first four paragraphs of it with the Communiqué dated 28.12.2018 have been the subject of objections and lawsuits.

- First of all, patient with macular degeneration (.....) (26.04.2019), AIFD (18.02.2019), BAYER (25.01.2019) and TOA (25.01.2019) submitted written objections to SSI. SSI replied to the objection applications that the relevant HIC change was made pursuant to the regulations of the Social Insurance and General Health Insurance Law No. 5510 (18.02.2019 and 20.02.2019).[15]

- Then, (.....) (2019/11670 E.), BAYER (2019/4118 E. and 2019/11654 E., two cases), NOVARTIS (2019/7580 E.) and TOA (2019/7438 E.) filed lawsuits before the 10th Chamber of the Council of State and then, essentially requested the stay and cancellation of the execution of the relevant regulations of Article 4.2.33. of HIC.

- In the lawsuits filed by NOVARTIS and TOA, requests for stay of execution were rejected by the Court's decisions dated 17.09.2019.

- According to the available information, ROCHE has not filed an objection to SSI regarding the issue and has not taken legal action.

I.2.11. TMMDA

(97) The response letter sent by TMMDA with the number 5659 and dated 11.06.2020 contains information about the lawsuits filed by NOVARTIS, BAYER and TOA.

(98) A lawsuit was filed by NOVARTIS against the SSI Presidency on 11.09.2019 with the number 2019/7580 for the stay of execution and annulment of the change made in article 4.2.33. of HIC, before the 10th Chamber of the Council of State; on 13.05.2019, the Council of State decided that the Ministry of Health should be taken as a defendant alongside SSI, and that the request for a stay of execution should be examined after the defenses of the defendants SSI and the Ministry of Health were received.

(99) The content of NOVARTIS' lawsuit petition includes the following briefly:

[15] The action taken regarding (.....)'s petition is unknown.

- With the change made in article 4.2.33. of HIC titled "Principles of Drug Use in Eye Diseases" on 28.12.2018, *Bevacizumab*, an oncology product not licensed for eye diseases, was made mandatory to be used as first-line treatment in the reimbursement system of the drug with ophthalmology indications neovascular AMD, diabetic macular edema, retinal vein occlusion and central retinal vein occlusion, and choroidal neovascularization due to pathological myopia,

- The aforementioned practice is contrary to legal regulations and precedent decisions of the Council of State, especially the Constitution, the Regulation on Licensing of Medicinal Products for Human Use published in the Official Gazette dated 19.01.2005 and numbered 25705, the OLDL Guide, which was edited by the Ministry of Health and changed over time, SSI Reimbursement Regulation published in the Official Gazette dated 10.02.2016 and numbered 29620, Patient Rights Regulation published in the Official Gazette dated 01.08.1998 and numbered 23420, the Regulation on Medical Deontology published in the Official Gazette dated 19.02.1960 and numbered 10436,

- *Bevacizumab* does not have a license approval or clinical study for its use in the treatment of eye diseases, and it is used in eye diseases in very exceptional and limited situations in various countries of the world,

- Active substances (*Ranibizumab*, *Aflibercept*, *Dexamethasone*, *Verteporfin*) other than *Bevacizumab* included in article 4.2.33. of HIC are licensed by the Ministry of Health for the treatment of various eye diseases,

- For diseases that can be treated with drugs within the approved indication in our country, off-label drug use is only possible if there are treatment options that provide significant advantages in line with scientific data, and *Bevacizumab* does not have a proven scientific advantage compared to other authorized active substances,

- In exceptional off-label use of *Bevacizumab* for eye diseases, many serious public health cases have been experienced in the world, serious infections have occurred due to the preparation of a product not designed for intravitreal use for application to the patient, and these infections have had consequences leading to blindness,

- Filling enough medicine from the *Bevacizumab* bottle containing a large amount of medicine and dividing it for each patient poses a health risk, because there is no infrastructure or authorized health institution that can help to carry out this process in a sterile way,

- In countries where there are no pharmacies that can legally and in a sterile way divide for each patient, the risk of intraocular infection increases to as high as 1 in 425 injections for drugs that are not approved for use in the eye when intravitreal administration is performed in hospitals, and this situation is very rare (1 in 7500-39,000 injections) for drugs approved for use in the eye,

- It is clearly stated in the SPC approved by the Ministry of Health that *Bevacizumab* can cause various degrees of vision loss when used for the eye,

- Off-label use of an unauthorized drug is exceptional, and it is a public health problem to make the use of off-label drugs a general practice when there is an authorized alternative,

- Despite scientific data, endophthalmitis cases and licensed alternatives, payment by SSI obliges the use of an unprocessed cancer drug instead of approved drugs,

- The right of physicians to freely determine the treatment to be administered

to their patients in accordance with scientific and medical standards is restricted and physicians are forced to treat patients with a drug that has the risk of blinding them,

- In 17.05.2013, the Ministry of Health stated that even the Ministry of Health itself would file a criminal complaint against physicians who use off-label drugs without complying with the rules, and within this scope, doctors who continue the current practice will face legal and criminal liability cases,

- The regulation made with the aim of reducing the cost of drugs in the short term poses irreparable risks in terms of public health, the widespread use of the drug for eye diseases may have negative consequences for cancer patients' access to the drug,

- *Bevacizumab* does not have sufficient and appropriate clinical research for authorization with respect to eye diseases, therefore it does not meet the authorization requirements in the Regulation on Licensing of Medicinal Products for Human Use; however, with the change made in HIC, its use as a first-line treatment for eye diseases is mandatory

- On 09.02.2019, the explicit rule of OLDL “If there is a treatment option with approved products in Turkey, off-label use cannot be allowed.” was removed and changed as "The use of off-label drugs for diseases that can be treated with drugs within the approved indication in our country is evaluated by the Institution only if there are treatment options that provide a significant advantage in line with scientific data"; however, when compared to other drugs licensed for eye diseases, *Bevacizumab* has no scientifically proven advantage and the HIC regulation is also against OLDL,

- Pursuant to the SSI Reimbursement Regulation, the effects of drugs on the budget, market shares, technical data and economic and financial data should also be taken into account when making changes in the reimbursement conditions of drugs, The Reimbursement Commission does not have unlimited discretion in this matter, and HIC was changed by considering the short-term cost savings without performing the reimbursement analysis.

(100) The draft response letter prepared by TMMDA based on the above case discussed the use of Anti-VEGF in other countries, drug efficacy and side effects comparisons, and the following is stated:

- In the USA and Israel, it is not possible to switch to other drugs without the use of three doses of *Bevacizumab* in the diagnosis of all retinal vascular diseases and AMD, and the use of *Bevacizumab* is off-label in the USA,

- Although off-label use of drugs is extremely common, generic drug manufacturers may not enter the high-cost FDA approval process for a new indication, *Bevacizumab* is one of the drugs with a long history of safety and efficacy although there is no FDA approval for ocular use,

- According to the American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) Survey, which is conducted annually, in 2018, *Bevacizumab* was the first drug preferred in the USA for AMD with a rate of 70.2%, and this rate increased to 79.3% in Africa and the Middle East, in Asia and Europe, *Bevacizumab* ranked second with 30.9%,

- According to the research conducted in 2017, *Bevacizumab* was the first drug preferred in the USA for central retinal vein occlusion with a rate of 68.6%, in Africa and the Middle East, the rate of preference for this drug was 68.1%, in Asia 41.1%, and in Europe, *Bevacizumab* ranked second with 24.7%,

- According to the research conducted in 2017, the first drug of choice for branch retinal vein occlusion was *Bevacizumab* with a rate of 70.2% in the USA, 69.2% in Africa and the Middle East, 39.7% in Asia and 26.7% in Europe,

- According to the ASRS PAT Research conducted in 2016, the first drug of choice for diabetic macular edema was Bevacizumab with a rate of 62.2% in the USA,

74.8% in Africa and the Middle East, 31.3% in Asia and 36.3% in Europe,

- In Italy, off-label use and reimbursement of *Bevacizumab* are available and the Court of Justice of the European Union (CJEU) ruled that the application could continue in the lawsuit filed for the cancellation of the application,

- In the guide published by the National Institute for Health and Care Excellence (NICE) in England on 23.01.2018, as a result of the comparison of anti-VEGF agents for the treatment of AMD, it was concluded that "…there is no clinically significant difference in efficacy and safety" between *Bevacizumab* and *Ranibizumab* and *Aflibercept*.

(101) After the above information, the following results regarding drug efficacy comparisons and side effects were included:

- In the CATT Study, IVAN Study, French Evaluation Group Avastin Versus Lucentis Study (GEFAL Study) and The Lucentis Compared to Avastin Study (LUCAS Study), which compared various treatment regimens for AMD, the results of *Bevacizumab* and *Ranibizumab* treatment regimens were found out to be similar,

- In the randomized multi-center Protocol T study of DRCR.net, which is one of the studies comparing anti-VEGF agents (*Ranibizumab*, *Aflibercept*, *Bevacizumab*) in the treatment of DME, all three agents were found to be similar,

- According to the studies conducted by the SCORE2 working group on patients with central retinal vein occlusion and secondary macular edema due to hemi-central retinal vein occlusion, no significant difference was found between the *Bevacizumab* group and *Aflibercept* group, and similar visual results were obtained with both drugs without a great difference in side effects,

- In the study by Khan M. et al., the effectiveness of *Ranibizumab* and *Bevacizumab* in retinal vein occlusion were compared, there was no difference between the number of injections and the final visual acuity in both groups,

- It was determined by many studies that different types of Anti-VEGF agents (*Bevacizumab* or *Ranibizumab*) do not affect the risk of endophthalmitis; randomized controlled clinical studies and meta-analyses, which are the most valuable scientific data, showed that there is no difference between anti-VEGF drugs in terms of endophthalmitis.[16]

(102) BAYER filed a lawsuit numbered 2019/4118 in the 10th Chamber of the Council of State on the annulment and stay of execution of the article 4.2.33 of HIC, which was changed with the article 25 of the Communiqué on the Amendment of the Social Security Institution's Health Implementation Communiqué, which came into

[16] Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of the literature. Eye (Lond). 2013 Jul; 27(7): 787-94; VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N) Clinical Trial Group. D'Amico DJ, Masonson HN, Patel M, et al. Pegaptanib sodium for neovascular age-related macular degeneration: Two-year safety results of the two prospective, multicenter, controlled clinical trials. Ophthalmology 2006; 113: 992-1001.

force after being published in the 1st repeated Official Gazette dated 28.12.2018 and numbered 30639, which is the basis of the Announcement Regarding the Regulations Made in Intraocular Drug Applications with Regard to the 2018/1st Term Drug Reimbursement Commission Decisions dated 05.03.2019 and published by SSI, and the administrative action dated 18.02.2019 and numbered E.2760731 established against the administrative application dated 28.01.2019 and numbered 1533568 against this regulation; pursuant to the status of the case and the legal nature of the dispute, it was decided to examine the request for stay of execution after the plea of the defendant administrations was presented or the legal defense period expired.

(103) TOA filed a lawsuit against the SSI Presidency on 11.09.2019 with the number 2019/7438 for the purpose of stay of execution and annulment of the change made in article 4.2.33. of HIC, in the 10th Chamber of the Council of State; on 25.04.2019, the Council of State decided to take the Ministry of Health as a defendant alongside SSI and to examine the request for a stay of execution after the pleas of the defendant SSI and the Ministry of Health were submitted.

(104) The following statements were included in the draft plea letter prepared by TMMDA, based on the lawsuit filed by TOA:

- OLDL, which is taken as a basis for application file to the court is not valid, and in February 2019, the paragraph with a translation error starting with the headline "not suitable for intravitreal use" was removed from the *Altuzan* SPC and updated as “not formulated for intravitreal use” as contained in the original English statement,

- The aforementioned statement in *Altuzan*'s SPC was removed with the decision of TMMDA dated 06.11.2018, because international institutions and organizations (including FDA) have taken up-to-date decisions allowing this use and not to cause confusion in clinical practice, although these actions took place before the date of filing the lawsuit, they were presented to the court as misinformation by the plaintiff,

- Before the SSI regulation, *Bevacizumab* active ingredient drug was reimbursed by SSI with off-label approval since 2014 and were used in many public and private hospitals,

- The process carried out by the Ministry of Health is not based only on economic reasons, the Ministry of Health presents its opinions by prioritizing the health dimension,

- Among the randomized clinical trials used to determine the efficacy of the drug in scientific drug researches, the most commonly used one is the *non-inferiority hypothesis*; *Ranibizumab*, *Aflibercept* and *Bevacizumab* studies were based on this hypothesis and clinical studies demonstrated that *Bevacizumab* was effective, not inferior, and provided an advantage,

- Drug applications are not given only to the initiative of physicians throughout the world and are controlled and regulated by regulatory institutions.

In the NOVARTIS case, the draft letter was included again.

I.3. The Relevant Market

I.3.1. The Relevant Product Market

(105) Within the scope of the investigation, whether *Altuzan* and *Lucentis* are in a substitution relationship with each other and therefore whether they are in the same relevant product market, is of great importance in terms of the determinations

and assessments to be made within the scope of the file. An assessment that these drugs are in the same relevant product market makes ROCHE and NOVARTIS direct competitors, while an assessment to the contrary results in the elimination of many competitive concerns addressed within the scope of the case.

(106) Considering the importance of the definition of the relevant product market in terms of the case, below, firstly, the information and opinions presented to the Board regarding the relevant product market by ROCHE, which currently controls GENENTECH, which develops the active substances of both products, and then, some scientific studies and authority decisions regarding whether the said active substances are substitutes for each other in the treatment of eye diseases are shown and finally, the information obtained from ophthalmologists is assessed in order to determine the demand-side substitution relationship.

I.3.1.1. Information and Opinions Provided by ROCHE on the Relevant Product Market

(107) In the document dated 20.05.2019 and numbered 3375 submitted to the Authority by ROCHE, detailed information about the development processes of *Altuzan* and *Lucentis* was given. According to the information provided, *Bevacizumab*, the active ingredient of *Altuzan*, was developed primarily for the field of oncology, and the use of this substance in the treatment of AMD was also investigated. As a result of the detection of some side effects in the intravenous or intravitreal use of *Bevacizumab* in the treatment of AMD, R&D studies continued, and *Ranibizumab*, the active ingredient of *Lucentis*, was developed for the treatment of AMD. Detailed information on this process is given below.

(108) Vascular Endothelial Growth Factor (VEGF) is a protein produced by human body and responsible for i) the growth and functioning of normal blood vessels, as well as ii) the formation of abnormal blood vessels that cause the growth of certain cancer tumors or macular degeneration. This protein was discovered by GENENTECH researchers, and in 1993 a murine antibody named A.4.6.1, capable of inhibiting the harmful effects of VEGF was discovered; subsequently, in 1996, an anti-VEGF monoclonal antibody, which was humanized, with the successful humanization of the murine antibody, and later called *Bevacizumab*, was developed.

(109) According to information provided by ROCHE, the main goal of development of *Bevacizumab* was primarily treatments for oncology, for which there were few treatments at the time, but other diseases were also studied during this research, including AMD, a common eye disease. It was concluded that the specificity of *Bevacizumab* for AMD treatment will not be easy due to i) the uncertainties about how the antibody can best be administered to the eye and ii) the uncertainty of the process that will ensure effective access to choroidal neovascular lesions, which should be followed especially when administering VEGF inhibitor to the patient.

(110) The possibility of administering *Bevacizumab* with intravenous injection (through a vein in the arm), which is the method of administration frequently used in related oncology indications, and thus reaching the eye by circulating the whole body, was assessed; however, this possibility was not accepted due to the long-term exposure of the whole body to *Bevacizumab* as a result of the intravenous injection method and the increased serious systemic (such as atherothrombotic and cardiovascular events that are not limited to the eye but affect the whole body) risks as a result of this situation.

(111) It was concluded that the application of *Bevacizumab* directly to the eye by intravitreal injection was safer and this method should be preferred in the treatment of ocular vascular disorders such as AMD; intravitreal administration raised some concerns regarding safety and efficacy due to the intraocular administration of a whole antibody such as *Bevacizumab* for the treatment of ophthalmic conditions.

(112) In addition, it was found that the half-life of *Bevacizumab*[17] of three weeks poses an important safety issue, and even if administered by intravitreal injection, *Bevacizumab* definitely enters the bloodstream (as in many drugs injected into the eye),and exposure of the whole body to *Bevacizumab* for a long period of three weeks significantly increases the risk of serious systemic side effects.

(113) Prolonged and systemic exposure of the body to *Bevacizumab* when treating a disseminated tumor is considered acceptable given the benefit-risk ratio of the drug and the severity of the disease and the potential consequences of *Bevacizumab* for patient survival; on the other hand, prolonged and systemic exposure of the body to *Bevacizumab* in the treatment of macular degeneration has been found to be unreasonable for elderly patients, who are more susceptible to the risks that may arise due to the long half-life of *Bevacizumab*.

(114) Additionally, findings from animal experiments by GENENTECH to ensure efficacy have shown that an entire antibody such as *Bevacizumab* does not provide perfect retinal penetration or adequate binding affinity due to its size, and for these reasons *Bevacizumab* has not been observed to provide optimal efficacy in the treatment of ocular vascular disorders. Due to the efficacy and safety problems in question, GENENTECH decided not to continue research and development (R&D) studies on the use of *Bevacizumab* in the ophthalmic field and to develop a different effective and safe anti-VEGF drug in this field.

(115) In this context, GENENTECH, in parallel with the development of *Bevacizumab* in the field of oncology, started to work on the development of an anti-VEGF that was targeted to be used in the field of ophthalmology, especially in the treatment of macular degeneration. Since the main purpose of these studies was to reduce the frequency of intravitreal injections, a substance that binds and inhibits VEGF at a higher rate than *Bevacizumab* in order to make an anti-VEGF of this nature, later called *Ranibizumab*, was developed. Two billion USD was invested by GENENTECH for the development of Ranibizumab, and significant costs were born by spending time and energy.

(116) *Ranibizumab* is approximately one-third the size of *Bevacizumab*, and by reaching its site of action with better retinal penetration leads to more effective treatment of ocular vascular diseases. Also, unlike the three-week half-life of *Bevacizumab*, *Ranibizumab* leaves the bloodstream within a few hours after application to the eye. In this case, as a result of the application of the drug, the systemic exposure of the human body is significantly reduced and the risks of serious side effects arising from long exposure are eliminated. In addition, while the content of *Bevacizumab* may cause inflammation that may damage the normal tissues in the eye, this side effect is not seen due to the content of *Ranibizumab*.

(117) In line with this information, Roche AG stated the following:

- Due to its half-life and content of Bevacizumab, it causes significant side

[17] The half-life of a drug is the time it takes for half of the administered amount of the drug to be removed from the bloodstream.

effects as a result of both intravenous injection (through a vein in the arm) and intravitreal method (direct injection into the eye),

- Ranibizumab was developed with significant costs to eliminate these side effects and provides more effective treatment compared to Bevacizumab,

- Therefore, Bevacizumab and Ranibizumab are two different products and cannot be substituted.

I.3.1.2. Information Obtained Regarding the Relevant Product Market within the Scope of the File

a) Information Obtained from Academic Studies

(118) AMD and DME are the main causes of blindness, for example, in the USA alone, more than 2 million people are known to have these diseases.[18]While the treatment of these diseases was not possible until the 2000s, with the development of anti-VEGF agents, many patients continued to see.[19] Anti-VEGF agents, which are complex molecules produced in living cells in a laboratory environment, treat the aforementioned diseases by suppressing the formation and growth of abnormal blood vessels in the retina. Both *Ranibizumab* and *Bevacizumab* were developed by GENENTECH, a current subsidiary of ROCHE.

(119) *Ranibizumab* has received FDA approval for use in patients with AMD and diabetic macular edema, while Bevacizumab has received FDA approval to treat various forms of systemic cancer. However, *Bevacizumab* is frequently used off-label in the treatment of the aforementioned ophthalmic diseases. Some ophthalmologists prefer *Bevacizumab* because of its price because, while the dose price of *Ranibizumab* is 2023 USD, the dose price of *Bevacizumab* is 55 USD. These amounts increase exponentially with each dose administered to the patient.[20]

(120) Spending on the use of *Ranibizumab* and *Bevacizumab* in the treatment of eye diseases in the USA has approached one-sixth of the Medicare Part B drug budget. The prices of these drugs, which have been proved by academic studies to have a similar efficacy level and not to show significant differences in terms of side effects, vary significantly. *Lucentis* costs US$ 2023 a dose, 40 times the price of one dose of *Avastin*. According to the study of Hutton et al., in which they applied various modeling methods based on the current use of the aforementioned drugs, it was found that if all patients had been treated with *Bevacizumab* instead of *Ranibizumab* between 2010 and 2020 in the USA, 18 billion USD could have been saved in terms of *Medicare Part B* expenditures and 5 billion USD in terms of patients; moreover, these savings could have be made without affecting the expected result from the treatment undergone by the patients.[21]

---

[18] Zhang X, Saaddine JB, Chou CF, Cotch MF, Cheng YJ, Geiss LS, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA. 2010;304 (6):649-56; Friedman DS, O'COLMAIN BJ, Moñoz B, Tomany SC, McCarty C, DeJong PT, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004; 122(4):564–72.

[19] See. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355 (14): 1419-31; Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006; 355 (14): 1432-44; Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012; 119(4):789–801.

[20] Department of Health and Human Services, Office of Inspector General. Medicare payments for drugs used to treat wet age related macular degeneration. Washington (DC): HHS; 2012 Apr 20.

[21] David Hutton, Paula Anne Newman-Casey, Mrinalini Tavag, David Zacks, and Joshua Stein,

(121) When the CATT Study[22] conducted on 1185 patients in 43 clinics in the USA between 2008 and 2010, which is the first of two clinical studies funded by the USA and including patients with neovascular AMD, was examined, the following was reached:

- AMD is the main cause of vision loss in patients over the age of 65 in the USA and other western countries,

- The aim of the study was to compare the efficacy and safety of *Lucentis* and *Avastin* in the treatment of AMD when administered to the patient with both a fixed program and a variable program,

- Prior to *Lucentis*, *Avastin*, an almost identical equivalent of *Lucentis*, was widely used by ophthalmologists in the treatment of AMD; the cost of treatment with *Avastin* was $50-100 versus $2000 for treatment with *Lucentis* and *Avastin* was molecularly similar to *Lucentis*, thus Avastin continued to be used after the development of *Lucentis*.

According to the two-year results of the aforementioned study, it was found that drugs had similar effects in the treatment of AMD, and that there was no difference between drugs in terms of mortality rates and arteriothrombotic events.

(122) Another study conducted on 610 patients between 2008 and 2010 was "*Ranibizumab versus Bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial*".[23] The aim of the study was to compare the efficacy and safety of intravitreal administration of *Ranibizumab* and *Bevacizumab* in the treatment of AMD; as a result of the study, it was found that the visual acuity was equivalent in the patients to whom both drugs were administered, and the other findings obtained in the study were consistent with the finding that these two substances had similar efficacy and safety.

(123) In addition, when various academic studies were examined within the scope of this investigation, it was seen that there were parallel results with CATT and IVAN Studies. For example, the GEFAL Study comparing Ranibizumab and *Bevacizumab* treatment options in the diagnosis of AMD compared the results of 1.25 mg PRN *Bevacizumab* treatment with 0.5 mg PRN *Ranibizumab* treatment. At the end of the first year, an increase in vision of 15 letters or more was observed in the groups at a rate of 20.4% and 21.3%, respectively. Considering the results of visual augmentation with less than fifteen letters, the rate was found to be 91.2% and 90.2%, respectively. In conclusion, when the first-year vision results were examined, it was reported that *Bevacizumab* is at least as effective as *Ranibizumab* and has a similar safety profile.[24]

"Switching To Less Expensive Blindness Drug Could Save Medicare Part B $18 Billion Over A Ten-Year Period", 10.1377/hlthaff.2013.0832 HEALTH AFFAIRS 33, NO. 6 (2014): 931–939.

[22] For detailed information about the study, see CATT Research Group, Martin DF, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012 Jul; 119(7): 1388-98, https://clinicaltrials.gov/ct2/show/NCT00593450, Access Date: 05.06.2020.

[23] IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus Bevacizumab to treat neovascular Age-Related Macular Degeneration: one-year findings from the Ivan randomized trial. Ophthalmology 2012; 119:1399-1411, https://www.ncbi.nlm.nih.gov/pubmed/22578446 , Accessed: 05.06.2020.

[24] Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. Ophthalmology 2013; 120:2300-2309.

(124) In the LUCAS Study, which compared the results of *Ranibizumab* and *Bevacizumab* TREX (Treat and Extend) treatment regimens in the diagnosis of AMD, patients were divided into two groups and treatment options of 0.5 mg *Ranibizumab* and 1.25 mg *Bevacizumab* were compared. At the end of the first year, an increase in vision of 15 letters or more was observed in the groups, at a rate of 26.7% and 25.2%, respectively. As a result, similar visual results were obtained with the *Bevacizumab* and *Ranibizumab* TREX treatment regimen at the end of one year.[25] In conclusion, it was reported that 2 mg of *Aflibercept* injection every two months and 0.5 mg of *Ranibizumab* administered monthly showed similar efficacy and safety.[26]

(125) One of the studies comparing anti-VEGF agents (*Ranibizumab*, *Aflibercept*, *Bevacizumab*) in the treatment of DME is the DRCR.net randomized, multicenter Protocol T study.[27] There was no significant difference in visual acuity gain with all three agents in those with good initial visual acuity. In the second year results, visual gains were similar in all three agents, including those with good initial visual acuity.

(126) In a clinical study of the SCORE2 study group for retinal vein occlusion, which included 362 patients with central retinal vein occlusion and secondary macular edema due to hemi-central retinal vein occlusion and evaluated whether there was equal efficacy by randomizing patients to 1.25 mg *Bevacizumab* (n: 182) and 2 mg intravitreal *Aflibercept* (n: 180), Scott et al., found no significant difference between the two groups, nor did they detect any evidence of confusion or bias that could explain the results. In this study, it was shown that *Bevacizumab*, which is used without a license, is as effective as *Aflibercept*.[28]

(127) In the study by Khan et al., the efficacy of *Ranibizumab* and *Bevacizumab* in retinal vein occlusion were compared, and no difference was found between the number of injections and the final visual acuity in both groups.[29]

(128) Despite all these studies, GENENTECH does not attempt to obtain FDA approval for the use of *Bevacizumab* for intraocular application in the treatment of eye diseases, on the grounds that *Ranibizumab* was developed specifically for the treatment of eye diseases.[30]

b)Information Obtained from Authority Decisions

---

[25] Berg K, Pedersen TR, Sandvik L, Bragadottir R, et al. (2016), “Comparison of Ranibizumab and Bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol” Ophthalmology 2016 Feb; 123(2):e14-e16, https://pubmed.ncbi.nlm.nih.gov/25227499/ . Access Date: 05.06.2020.

[26] Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012; 119(12):2537-48.

[27] Wells JA, Glassman DEC, Ayala DEC, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123(6):1351-1359.

[28] Scott IU, VanVeldhuisen PC, IpMS, Blodi BA, Oden NL, Awh CC et al; SCORE2 vestigator Group. The effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. JAMA. 2017; 317(20): 2072-2087.

[29] Khan M, Wai KM, Silva FQ, Srivastava S, Ehlers JP, Rachitskaya A, et al. Comparison of Ranibizumab and Bevacizumab for Macular Edema Secondary to Retinal Vein Occlusions in Routine Clinical Practice. Ophthalmic Surgical Lasers Imaging Retina. 2017;48(6):465-472.

[30] Whoriskey P, Keating D. (2013), “An effective eye drug is available for $50. But many doctors choose a $2,000 alternative” Washington Post, https://www.washingtonpost.com/business/economy/an- effective-eye-drug-is-available-for-50-but-many-doctors-choose-a-2000- alternative/2013/12/07/1a96628e-55e7-11e3-8304-caf30787c0a9_story.html, Accessed: 05.06.2020.

(129) Under this heading, instead of separately mentioning the decisions of the authorities in the fields of medicine and competition regarding *Avastin* and *Lucentis*, the issues mentioned by the Commission in its report titled “Study on the Off-Label Use of Medicinal Products in the European Union” (Commission Study)[31] published in February 2017 will be shown. The following issues were addressed in the Commission's Study:

(130) *Avastin* is a drug whose active ingredient is *Bevacizumab*. *Bevacizumab*, as a humanized anti-VEGF monoclonal antibody, binds to VEGFs and inhibits angiogenesis, especially in cancer. *Avastin* was registered in January 2005 as the primary-care for the treatment of patients with metastatic carcinoma of the colon and rectum.

(131) Angiogenesis is also seen in some eye diseases such as AMD, and substances such as *Bevacizumab* may therefore be effective in the treatment of these diseases. *Macugen* and *Lucentis* both contain an angiogenesis inhibitor as an active ingredient. These are, respectively *Pegaptanib* and *Ranibizumab*. *Macugen*[32] was registered in Europe in 2006 and *Lucentis* in 2007 for the treatment of macular degeneration. Prior to the registration of *Macugen* and *Lucentis*, *Avastin* was used off-label and recognized as an effective treatment for macular degeneration. Prior to *Lucentis* and *Macugen*, the main reason *Avastin* was used to treat macular degeneration was that there was no authorized drug available to treat AMD at the time.

(132) With the approval of *Macugen* by the EMA in 2006, ophthalmologists observed that this drug had less efficacy and worse-than-expected results in some patients. This led to further investigation of the off-label use of *Avastin* in patients who did not respond to *Macugen* and photodynamic therapy, which were limited treatment modalities at that time. The main reason for the use of *Avastin* in the presence of *Macugen* was not because there was no alternative, but because the off-label use of *Avastin* provided more effective results than the use of *Macugen* within the approved indication. However, with the registration of *Lucentis* in 2007, the main motivation for the use of *Avastin* changed again. *Macugen* stabilizes vision loss, while *Lucentis* prevents the progression of vision loss and also increases visual acuity. However, the price of *Lucentis* is higher than that of *Macugen*.

(133) For this reason, it has long been a matter of debate whether *Lucentis* will be reimbursed by the health system. Roche AG tried to prevent off-label use by emphasizing the safety risks that may arise in case of off-label use of *Avastin*[33], but did not directly compare the effectiveness of *Lucentis* and *Avastin*. As a result, studies were conducted with public research resources to prove that these two drugs were actually equivalent in terms of safety and effectiveness in the treatment of macular degeneration. In consequence of these studies, that *Bevacizumab* and *Ranibizumab* were found to be equivalent, and *Avastin* became the product of choice in the

---

[31] ttps://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf , p. 56, Accessed: 05.06.2020.

[32] For detailed information about Macugen product, see https://www.pfizer.com.tr/sagliginiz-icin/macugen%C2%AE-03-mg90-%C2%B5l-l-intravitreal-kullan%C4%B1m-i%C3%A7in-enjekt%C3%B6r, Accessed: 05.06.2020.

[33] Health Canada Supported Important Safety Information on Avastin (Bevacizumab). Retrieved on March 2016 from http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14494a-eng.php,

treatment of AMD in the Netherlands[34].

(134) In 2014, ICA fined Novartis AG and Roche AG for spreading misinformation about the more affordable *Avastin*, which, by mutual agreement, shifted the demand to *Lucentis*. In June 2014, the Italian Medicines Agency included *Avastin* in its reimbursement list for AMD treatment.[35] In 2014, France removed *Lucentis* from the reimbursement list and replaced it with *Avastin*.

(135) In June 2015, the French Medicines Agency published a recommendation for the use of *Avastin* in the treatment of AMD, valid for three years from 01.09.2015.[36]

(136) In addition, the use of Avastin in the treatment of AMD is recommended by the World Health Organization.[37] On the other hand, Novartis AG, Roche AG and the European Federation of Pharmaceutical Industries and Associations (EFPIA) argued that the decision to prescribe an off-label drug should be based on medical needs rather than economic concerns.[38]

(137) At this point, it is worth mentioning the ICA's decision: with its decision on 27.02.2014, ICA fined Roche AG and its subsidiary Roche Italy a total of 90.6 million Euros, and Novartis AG and its subsidiary Novartis Italy a total of 92 million Euros, on the grounds that they create an unrealistic difference between the drugs called *Avastin* and *Lucentis* by manipulating the risk perception in the use of *Avastin* by patients in the field of ophthalmology, with the agreement between Roche AG and Novartis AG.[39]

(138) On appeal of the ICA's decision, the Italian Council of State requested the Court of Justice of the European Union (CJEU)'s opinion on some issues regarding the interpretation of Article 101 of the TFEU. CJEU expressed the opinion that if there is a concrete substitution relationship between a drug used off-label and a drug used within indication of the same disease in principle, they can be included in the same relevant product market. This opinion confirms the evaluation of ICA regarding the relevant product market that *Avastin* and *Lucentis* are in the same relevant product market. The ICA, on the other hand, considered that the two drugs were in the same relevant product market, mainly because ophthalmologists saw the two drugs as substitutes in terms of the treatments they applied and there were indications in the documents[40] obtained as part of the investigation conducted that

---

[34] Solomon SD, Lindsley KB, Krzystolic MG, et al. Intravitreal Bevacizumab Versus Ranibizumab for Treatment of Neovascular Age-Related Macular Degeneration: Findings from a Cochrane Systematic Review. Ophthalmology 2016;123 (1):7077.e1.

[35] Italy to The Fund Unapproved Use of Roche Drug to Cut Costs (2016) http://www.bloomberg.com/news/articles/2014-06-10/italy-to-fund-unapproved-use-of-roche- drug-to-cut-costs, Accessed: 08.06.2020.

[36] L'ANSM établit la RTU d'AVASTIN® (Bevacizumab) dans la dégénérescence maculaire liée à l'age (DMLA) dans sa forme néovasculaire - Point d'information (2017), http://ansm.sante.fr/S-informer/Points- d-information-Points-d-information/L-ANSM-etablit-la-RTU-d-Avastin-Rbevacizumab-dans-la- degener tu-maculaire-liee-a-l-age-DMLA-dans-sa-forme-neovasculaire-Point-d-information, Accessed: 08.06.2020.

[37] https://www.who.int/selection_medicines/committees/expert/21/reviews/Bevacizumab_Review2.pdf and https://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf, Accessed: 05.06.2020

[38] ROCHE, NOVARTIS protest moves in EU to pay for off-label Avastin (2016), http://www.fiercepharma.com/story/roche-novartis-protest-moves-eu-pay-label-avastin/2014-07-28, Accessed: 05.06.2020.

[39] The Roche/Novartis Decision of the Italian Competition Authority dated 27.02.2014 (Case I-760).

[40] The above mentioned decision. para. 179-180

Novartis was worried that the sales of *Lucentis* would be gradually destroyed due to the increase in *Avastin* sales.

(139) The parties claimed that the ICA didn't identify the relevant product market correctly, and that the regulatory framework prevented the establishment of a substitution relationship between a drug used off-label for a particular indication and an authorized drug. Italian Council of State, taking into account the opinions of the CJEU, rejected this claim of the parties on the grounds that sector regulations did not prevent the off-label use of *Avastin* and even its repackaging in smaller doses for off-label use.

(140) The fact that ICA's definition of the relevant product market is based on the demand-side substitution relationship has been criticized by some circles.[41] The basis of the criticism is that the demand for *Avastin* in the treatment of eye diseases in Italy is not a direct preference of doctors, *Avastin* is used off-label for economic reasons by doctors and this is against EU legislation. According to EU legislation, the off-label use of a drug is very limited[42], pharmaceutical companies are expressly prohibited from promoting the off-label use of a drug.[43] However, the relevant legislation does not justify the fact that the parties shifted the request to *Lucentis* by spreading misinformation among doctors, public institutions and the public, raising concerns about *Avastin*'s risks.

(141) In addition to the ICA's decision, there is also a judicial decision in the United Kingdom regarding the interchangeability of *Avastin* and *Lucentis*. *Avastin*, which costs £28 per injection in the UK, is widely used in the treatment of AMD, but is only authorized for the treatment of cancer. The unit cost of *Lucentis*, a licensed product of NOVARTIS in the treatment of AMD, is 561 Pounds, and the cost of *Eylea*, an authorized product of BAYER, is 800 Pounds. In northern England, 12 NHS Clinical Commission Groups (CCGs) have made a policy decision to prescribe *Avastin* because it is as effective as other drugs in the treatment of AMD and is relatively affordable. BAYER and NOVARTIS filed a lawsuit in the London High Court seeking judicial review of the policy of the 12 NHS Clinical Commission Groups (CCGs) to prescribe *Avastin* for the treatment of AMD in northern England. Judge Whipple rejected the claim of the Clinical Commission Groups of BAYER and NOVARTIS to review the policy, considering that the CCGs' policy was based on the price difference between drugs and that this was reasonable as the drugs could be used interchangeably.[44]

c)Information from Ophthalmologists

(142) When the response letters from (.....) are compiled, the following points are understood:

- Ophthalmologists use *Altuzan* and *Lucentis* as anti-VEGF agents in the treatment of the same eye diseases,

---

[41] Killick J and Pascal B (2015), Pharmaceutical Sector: Can Non-Authorised Products be Included in the Relevant Market for the Assessment of Alleged Anticompetitive Conduct? A Short Analysis of the Recent Italian Avastin-Lucentis Decision

[42] A drug can be used off-label in approved clinical studies or in exceptional cases specified in Directive 2001/83 or Regulation 726/2004.

[43] Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to the medicinal products for human use, OJ (2001) L 311/67, Arts 86 and 87.

[44] In the High Court of Justice, Queen's Bench Division Administrative Court, Neutral Citation Number: [2018] EWHC 2465 (Admin), Case Nos: CO/5288/2017, CO/5357/2017, London, https://www.bailii.org/ew/cases/EWHC/Admin/2018/2465.html , Accessed: 08.06.2020.

- After the HICamendment dated 28.12.2018, the use of *Altuzan* has increased in general, excluding university hospitals,

- Although the division of *Altuzan* into doses is done in the operating rooms, the filling of the drug from the vial into the injector increases the risk of contamination for each patient,

- If it is possible to present *Altuzan* in a sterile injector that can be administered to a single patient, like other drugs, such concerns can be avoided,

- It has been heard that there are cases of malpractice related to the use of *Altuzan*, the physicians believe in the efficacy of *Altuzan*, but they are concerned that the use of *Altuzan* may constitute a medical malpractice,

- Although the physician is allowed to take initiative and administer a single vial of *Altuzan* to a patient and discard the remaining doses pursuant to HIC, the physicians are informed that this may cause problems in cancer patients' access to *Altuzan*, thus, if *Altuzan* is to be used in the eye, it is divided into doses so that the drug is not wasted,

- It is implied by the drug marketing authorities that the use of this drug may cause medical malpractice, based on the absence of an indication that it can be used in the eye in the *Altuzan* package insert.

(143) As can be seen, the concerns of ophthalmologists regarding *Altuzan* are generally that the drug is used off-label and medical malpractice cases may be encountered if divided into doses. None of the informing physicians mentioned the ineffectiveness or side effects of *Bevacizumab* contained in *Altuzan* as an anti-VEGF agent in the treatment of eye diseases. The fact that an application for a license has not been made for *Altuzan* in the treatment of eye diseases by ROCHE and the various risks and concerns arising from the fact that *Altuzan* is not packaged according to the doses used in eye diseases do not mean that *Bevacizumab* is a worse drug than *Ranibizumab* in terms of its efficacy in treatment and the severity of its side effects. The fact that *Lucentis* was used at higher rates compared to *Altuzan* by ophthalmologists before 28.12.2018 is also insufficient to show that *Altuzan* is less effective. In addition, according to the information obtained from various institutions within the scope of the case, sometimes infection risks may arise during the administration of drugs *Lucentis* and *Eylea* (Document-90).

(144) As a result, when the information provided within the scope of the Commission Study, the relevant authority decisions and the information obtained from ophthalmologists are assessed together, it is concluded that *Altuzan* and *Lucentis* can be used as substitutes for each other, and it is even considered that preferring *Altuzan* over *Lucentis* due to its lower price will be beneficial in terms of reducing the public's drug expenditures.

(145) In this framework, the relevant product market has been defined as *"anti-VEGF molecules applied intraocularly"*. Currently, the drugs covered by this market definition in the Turkish market are *Altuzan*, *Lucentis* and *Eylea*.

I.3.2. Relevant Geographical Market

(146) Actions and practices that are the subject of the investigation, and administrative acts and regulations affecting them concern the whole of Turkey and create results at this level. Actions such as trying to shift demand from competing anti-VEGF drugs to *Lucentis*, giving doctors negative publicity about *Altuzan*, or directing administrative processes with misleading information did not occur only in certain

regions or targeted certain regions. Therefore, since there is no fact that requires the definition of a market at the regional level, the relevant geographical market is defined as "Turkey".

I.4. Assessment

(147) In summary, it is stated in the complaint application that Roche AG and Novartis AG companies have derived unfair profits by engaging in cartel activities in order to increase the use of *Lucentis*, which is the more expensive of the drugs called *Altuzan* and *Lucentis* used in eye diseases; however, long before Lucentis was approved, the off-label use of *Altuzan* in the treatment of AMD by injecting it into the eye became widespread; ICA detected that Roche AG and Novartis AG agreed with each other to raise and spread concerns about the safety of ophthalmic use of *Altuzan* in order to increase the sales of *Lucentis*, and imposed administrative fines on the parties.

(148) The assessment made on the subject of the investigation is given below:

I.4.1 The Existence of t he Violation

(149) In SSI's written statement, it is stated that *Avastin* was used in ocular treatments in 2005 for the first time, that *Ranibizumab* in AMD in 2006, *Aflibercept* was approved by FDA in 2011 and licensed in 2014, hence the oldest use among anti-VEGFs is *Bevacizumab*. In Turkey, where the situation is similar, *Lucentis* was licensed for the first time in 27.03.2008, however, *Altuzan* which was licensed in 22.12.2015 was included in OLDL for ocular treatments in 2007. It is also known that before this date, *Altuzan* could still be used in ocular treatments but with the approval of the Ministry. Therefore, *Bevacizumab* was the first anti-VEGF agent ever used in related ocular treatments in the world and in Turkey.[45]

(150) There are plenty of studies that shows that *Bevacizumab* did not differ statistically on a significant level from *Ranibizumab* and *Aflibercept* in terms of efficiency and that they are also similar in terms of side effects.[46] Within the scope of the file, numerous academic studies comparing different treatment regimens according to the diagnosis of diseases have been reviewed. Within the scope of research comparing various treatment regiments in diagnosis of AMD such as

- CATT Research[47],

---

[45] David Hutton, Paula Anne Newman-Casey, Mrinalini Tavag, David Zacks, and Joshua Stein, *"Switching To Less Expensive Blindness Drug Could Save Medicare Part B $18 Billion Over A Ten-Year Period"*, 10.1377/hlthaff.2013.0832 HEALTH AFFAIRS 33, NO. 6 (2014): 931.

[46] E.g., see. 1) Berg K, Pedersen TR, Sandvik L, Bragadottir R, et al. (2016), *"Comparison of Ranibizumab and Bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol"* Ophthalmology 2016 Feb; 123(2):e14-e16, https://pubmed.ncbi.nlm.nih.gov/25227499/. Accessed: 05.06.2020; 2) Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. (2013), *"Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial"*Ophthalmology 120: 2300–2309 ; 3) Schauwvlieghe AME, Dijkman G, Hooymans JM, Verbraak FD, Hoyng CB, et al. (2016), *"Comparing the Effectiveness of Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration"*, The BRAMD Study. PLOS ONE 11(5): e0153052, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0153052. Accessed: 05.06.2020.

[47] CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results. Ophthalmology 2012;119(7):1388-98.

- IVAN Research[48],
- GEFAL Research[49]
- LUCAS Research[50] ,

the results of *Bevacizumab* and *Ranibizumab* along with treatment regimens have shown similarities.

(151) In addition, all three agents were found to be similar in the randomized multicenter Protocol T study of DRCR.net, which is one of the studies comparing anti-VEGF agents in the treatment of DME (Diabetic Macular Edema).[51] According to studies of SCORE2 Study Group on secondary macular edema due to central retinal vein occlusion and hemi-central retinal vein occlusion, no significant differences were detected among *Bevacizumab* group and *Aflibercept* group, and similar visual results were obtained with both drugs with no major differences in side effects.[52] In the study conducted by Khan M. et al., the efficiency of *Ranibizumab* and *Bevacizumab* in retinal vein occlusion was compared, and no differences were found between the number of injections and resulting visual acuity in both groups.[53]

(152) In line with academic studies, when physician practices and usage rates are taken into account, it is understood that in intraocular treatments, *Bevacizumab* is highly preferred in many countries, and even ranks first in terms of use in many countries/continents. Some of the findings on this subject matter are as follows:

- As of the beginning of 2020, *Bevacizumab,* the most popular Anti-VEGF molecule in the USA, is the first choice in the diagnosis of AMD (70.2%).[54]

- In Netherlands, while 75-80% of the intraocular injections are made with the mentioned active substance, the same rate is 90% in Bulgaria and 35% in Germany.[55]

- According to the ASRS PAT Research, in 2018, *Bevacizumab (Avastin)* was first active substance preferred in AMD with rates 70.2% and 79.3%, respectively

---

[48] The IVAN study investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration. Ophthalmology 2012; 119:1399-1411.

[49] Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, et al. Ranibizumab
versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. Ophthalmology 2013; 120:2300-2309.

[50] Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology 2015; 122:146-152.

[51] Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123(6):1351-1359.

[52] Scott IU, VanVeldhuisen PC, IpMS, Blodi BA, Oden NL, Awh CC et al; SCORE2 vestigator Group. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. JAMA. 2017; 317(20): 2072-2087.

[53] Khan M, Wai KM, Silva FQ, Srivastava S, Ehlers JP, Rachitskaya A, et al. Comparison of Ranibizumab and Bevacizumab for Macular Edema Secondary to Retinal Vein Occlusions in Routine Clinical Practice. Ophthalmic Surg Lasers Imaging Retina. 2017;48(6):465-472.

[54] Curtis LH, Hammill BG, Qualls LG, DiMartino LD, Wang F, Schulman KA et al. Treatment patterns for neovascular age-related macular degeneration: analysis of 284 380 medicare beneficiaries. Am J Ophthalmol 2012; 153: 1116–24.e1.).

[55] Bro T, Derebecka M, Jørstad ØK, Grzybowski A. Off-label use of bevacizumab for wet age-related macular degeneration in Europe. Graefes Arch Clin Exp Ophthalmol. 2019 Dec 30. doi: 10.1007/s00417-019-04569-8.

in the USA and Africa. In Asia and Europe, however, *Bevaizumab* ranks second with 30,9%.[56]

- According to the research conducted in 2017, *Bevacizumab* was the first choice in the USA and Africa (68.6% and 68.1%) in the diagnosis of central retinal vein occlusion while in Asia and Europe, these values are 41.4% and 24.7% respectively.[57]

- According to the research conducted in 2017, the first active substance preferred in the diagnosis of branch retinal vein occlusion was *Bevacizumab* with the rates 70.2% in the USA, 69.2% in Africa and the Middle East, 39.7% in Asia, and 26.7% in Europe.[58]

- According to the research conducted in 2016, the first active substance preferred in the diagnosis of diabetic macular edema was *Bevacizumab* with the rates 62.2% in the USA, 74.8% in Africa and the Middle East, 31.3% in Asia, and 36.3% in Europe.[59]

(153) In addition to the findings about the usage rates of the drugs mentioned, the opinions of associations of undertakings in various countries, public regulations and court decisions also attract attention:

- Council for Choices in Health Care in Finland has noted that *Bevacizumab* is an effective treatment for improving vision in AMD and is on par with *Ranibizumab* and *Aflibercept* in terms of efficacy and safety.[60]

-The German and Swedish Ophthalmological Societies have approved the effectiveness of *Bevacizumab* and stated that it is similar to *Ranibizumab.*[61]

- The Norwegian Ophthalmological Society recommends *Bevacizumab* as the first line therapy for neovascular AMD.[62]

- As the result of the comparison of anti-VEGF agents for the treatment of AMD in the guide published by the National Institute for Health and Care Excellence (NICE) on 23.01.2018 in England, it was concluded that there is no clinically significant difference in terms of "…efficacy and safety" between *Bevacizumab, Ranibizumab* and *Aflibercept*.[63] Also, as previously stated, a lawsuit filed by BAYER

---

[56] SRS Global Trends in Retina (2018), https://www.asrs.org/content/documents/2018-global-trends-in-retina-survey-highlights-website.pdf , Accessed: 08.06.2020.

[57] ASRS Global Trends in Retina (2017), https://www.asrs.org/content/documents/2017-asrs-global-trends-in-retina-survey-results.pdf , Accessed: 08.06.2020

[58]ASRS Global Trends in Retina (2017), https://www.asrs.org/content/documents/2017-asrs-global-trends-in-retina-survey-results.pdf , Accessed: 08.06.2020.

[59] ASRS Global Trends in Retina (2016), https://www.asrs.org/content/documents/2016_global_trends_in_retina_survey_highlights_for_website_2.pdf , Date Accesed: 08.06.2020.

[60] Council for Choices in Health Care in Finland (2015) The treatment of wet age-related macular degeneration with bevacizumab injection in the eye belongs to the publicly funded service choices in health care in Finland. https://palveluvalikoima.fi/en/recommendations , Accessed: 08.06.2020.

[61] German Ophthalmological Society & Retinological Society & Association of Ophthalmologists in Germany (2007) Statement of the German Ophthalmological Society, the Retinological Society and the Association of Ophthalmologists in Germany on current therapeutic options in neovascular age-related macular degeneration https://www.dog.org/wp-content/uploads/2009/08/DOG_Statement_AMDTherapy.pdf , Accessed: 08.06.2020.

[62] Norsk oftamologisk forening (2017) Nasjonal kvalitetshåndbok for oftalmologi. https://www.helsebiblioteket.no/retningslinjer/oftalmologi/forord , Accessed: 08.06.2020.

[63]The Royal College of Ofthalmologists (2018), "New NICE Age Related Macular Degeneration guidance

and NOVARTIS in Hig h Court of Justice in London to seek judicial review of the policy decision of twelve Clinical Commissioning Groups (CCGs) to prescribe *Avastin* due to the fact that it is as effective as other drugs in the treatment of AMD and is relatively affordable compared to others was rejected by the Judge Whipple on the grounds that the policy followed by the CCGs was based on the price difference between drugs and this was reasonable as the drugs could be used interchangeably.[64]

- As of the beginning of 2020, in the USA and in Israel, it is not possible to switch to other drugs without using three doses of *Bevacizumab* in the diagnosis of all retinal vascular diseases and age-related macular degeneration.

- In France, Novartis AG and Roche AG filed a lawsuit against off-label recommendations and claimed that the infection risk is higher for *Bevacizumab* than it is for *Ranibizumab*. Furthermore, in 2017, the French Administrative Supreme Court upheld the decision to support the ophthalmic use of *Bevacizumab.*[65] Also, in 2015, the French Agency for the Safety of Medicines and Health Products supported its ophthalmic use by listing *Bevacizumab* as off-label and this recommendation was renewed for three more years in 2018.[66]

-In Italy, *Bevacizumab* is currently used off-label and reimbursed. The CJEU ruled that the practice could continue in the lawsuit filed for the termination of the practice.[67]

(154) While the chronology of the events, academic studies and doctor practices as well as the opinions of the associations of undertakings in various countries, public regulations and court decisions promote the use of *Bevacizumab* in intraocular treatments, ROCHE's failure to actively assess its sales potential in this area is incomprehensible in terms of the strategic choices and commercial interests of an undertaking that is expected to act independently. Because for *Bevacizumab* which has a serious price advantage when compared to *Ranibizumab*, it should be expected that steps be taken to evaluate the aforementioned income potential in commercial terms whereas ROCHE acts in the opposite direction, arguing that its product is not suitable for use in related treatments, does not request the addition of these indications to the license, and does not develop single-use forms for these treatments. NOVARTIS, on the other hand, practices negative promotion about rival product *Avantis/Altuzan* before physicians and public authorities and raises objections in administrative and judicial processes.

(155) In 2014, ICA fined ROCHE and NOVARTIS over 90 million Euros separately. The reason for this decision was shown as the attempts of the

---

supports potential cost savings for the NHS", https://www.rcophth.ac.uk/2018/01/new-nice-age-related-macular-degeneration-guidance-supports-potential-cost-savings-for-the-nhs/ , Accessed: 08.06.2020.

[64] In the High Court of Justice, Queen's Bench Division Administrative Court, Neutral Citation Number: [2018] EWHC 2465 (Admin), Case Nos: CO/5288/2017, CO/5357/2017, London, https://www.bailii.org/ew/cases/EWHC/Admin/2018/2465.html, Accessed: 08.06.2020.

[65] Conseil d'État (2017) N°392459. https://www.legifrance.gouv.fr/affichJuriAdmin.do?oldAction=rechJuriAdmin&idTexte=CETATEXT000034081845&fastReqId=1568863364&fastPos=12

[66] L'Agence nationale de sécurité du médicament et des produits de santé Liste des spécialités faisant l'objet d'une RTU. https://www.ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Liste-des-specialites-faisant-actuellement-l-objet-d-une-RTU/(offset)/1 , Accessed: 08.06.2020

[67] Kelly D., 2018. European Court Rules in Favor of Allowing Off-label Bevacizumab Use. (https://www.centerforbiosimilars.com/news/european-court-rules-in-favor-of-allowing-offlabel-bevacizumab-use).

aforementioned undertakings to create a perception of difference that *Avastin* and *Lucentis* are different, which does not reflect the truth. According to ICA, both products have similar efficacy in the treatment of ocular diseases. ICA, have made the evaluation that undertakings caused a cost increase of 45 million Euros in the Italian health system in 2012 alone, by disseminating information to raise concerns about the safety of *Avastin* in its use in ophthalmology, shifting demand to *Lucentis*. After the Regional Administrative Court, to which the undertakings applied for the nullity of judgement, rejected the case, the undertakings have appealed to the Italian Council of State and immediately afterwards the case was examined within the scope of EU competition law and was referred to the CJEU for a preliminary ruling.

(156) The CJEU, considered that the coordination between two undertakings marketing two competing products based on spreading misinformation regarding the side effects of off-label use of *Avastin* to the European Medicines Agency, physicians and the general public, leading to scientific uncertainty, in order to reduce the competitive pressure on *Lucentis* as a restriction of competition by object. In addition, the CJEU stated that the aforementioned agreement cannot benefit from the exemption under TFEU art. 101(3), as the dissemination of misinformation about a drug is not a mandatory restriction.[68] At the end of the appeal process, it is seen that the Italian Council of State rejected the parties' case in July 2019.

(157) There are also various authority decisions in which the dissemination of misinformation about a product by rival undertakings following a common strategy is considered as a violation under competition law.[69] Specific to the decision taken by the ICA, it is seen that the undertakings benefit by disseminating misinformation to the relevant authorities and abusing legal regulations in order to achieve their anticompetitive purpose.

(158) ICA found

i) E-mail correspondence between the chairman of the board of directors (CEOs) at the ROCHE and NOVARTIS Italy branches, which clearly indicates that the differences between *Avastin* and *Lucentis* do not reflect reality,[70]

ii) Internal correspondences in a similar scope in ROCHE Italy,[71]

iii) Internal documents indicating that NOVARTIS will draw attention to the risks associated with the ophthalmic use of *Avastin* by funding various scientific symposia and international academic studies and communicating with patient groups within this context.[72]

According to internal documents of Novartis Italy, while independent comparative academic studies may allow ophthalmologists to use *Avastin* safely, this effect of academic studies has been minimized with the efforts of Novartis AG and

---

[68] CJEU Press Release, No: 06/18, Judgment in Case C-179/16 F. Hoffmann-La Roche Ltd and Others v Autorità Garante della Concorrenza e del Mercato, https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-01/cp180006en.pdf . Accessed: 05.06.2020.

[69] Spanish Competition Authority, S/0256/10 Inspecciones Periódicas de Gas Kararı (2012); French Competition Authority, n° 13-D-11 Sanofi-Aventis Decision, 2013.

[70] The Roche/Novartis decision of the Italian Competition Authority dated 27.02.2014 and numbered 24823, para. 193.

[71] The said decision para. 106-108.

[72] The said decision para. 196-199

Roche AG.[73] Fundamentally, it is seen that the national priorities declared by parent companies Roche AG and Novartis AG to their Italy branches are pursued by Roche Italy and Novartis Italy.[74] Therefore, in some countries including Turkey, it is clear that ROCHE and NOVARTIS are carrying out this global strategy.

(159) As stated in the section introducing the parties, Novartis AG holds a non-controlling interest of Roche AG's shares. Therefore, there is a shareholding relationship between ROCHE and NOVERTIS which are in independent undertakings. On the other hand, *Bevacizumab* and *Ranibizumab* have been developed by GENENTECH, a wholly owned subsidiary of ROCHE AG. GENENTECH has transferred the marketing and sale rights of *Avastin (Altuzan)* which contains *Bevacizumab* to ROCHE, the same rights of *Lucentis* which contains *Ranibizumab* to NOVARTIS outside of the USA. According to the license agreement signed between GENENTECH and NOVARTIS, NOVARTIS (.....) pays GENENTECH and indirectly to ROCHE.

(160) At this point, it is possible to say that the legal and commercial relations between the parties to the investigation form the financial basis of the global strategy mentioned above, which is also reflected in the Turkish medicine for human use market because ROCHE earns a significant income from the sales of *Lucentis*, a rival of its own product which is much higher priced. It is clear that this situation will diminish/ maybe even destroy the incentive to actively evaluate the sales potential of ROCHE's *Altuzan* which is widely preferred in the same treatment fields. Furthermore, it is obvious that the widespread use of *Lucentis,* which is a much higher priced product, instead of *Altuzan* will increase total sales and the drug expenditures in the relevant market.

(161) Looking at the case summarized regarding the worldwide situation at the Turkish level, it is understood that the parties to the investigation acted as in the case examined in Italy. Firstly, since 2007, when *Altuzan* was included in EDIL for intraocular treatments for the first time, ROCHE did not made any attempts to license and actively market this product in relevant indications, preferring to remain passive.

(162) In 2011, ROCHE also applied to add the phrase "*Altuzan is not suitable for intravitreal use."* to the SPC and PIL of this product. After the change of SPC and PIL of *Altuzan,* in 2018, TMMDA requested that this phrase be removed and ROCHE resisted this request for a long time. After TMMDA reported that the licenses of 100 mg and 400 mg forms of *Altuzan* could be suspended in this case, TMMDA's request was fulfilled in 2019. What is striking at this point is that the relevant phrase in the original reference document of the product is "*Avastin is not formulated for intravitreal use".* As a matter of fact, this expression was used in the global declaration letter that ROCHE notified TMMDA during the administrative process on the 2018-2019 SPC/PIL front.

(163) However, the fact that a drug is not suitable for intraocular use does not mean that it has not been formulated for it. In fact, as in the *Altuzan* example, it is possible for a drug to be suitable for intraocular use, even though it has not been

[73] The said decision para. 116.
[74] The Avastin Lucentis case: an illicit agreement between Roche and Novartis condemned by the Italian Antitrust Authority. Available from: https://www.researchgate.net/publication/307731444_The_Avastin_Lucentis_case_an_illicit_agreement_between_Roche_and_Novartis_condemned_by_the_Italian_Antitrust_Authority . Accessed: 05.06.2020.

developed for intraocular use. The different translation from the original reference document mentioned is considered to be a part of a strategy to disseminate misinformation about *Avastin/Altuzan,* as will be explained in detail below. As a matter of fact, this statement in SPC/PIL and other statements made in support of this were used as a basis for both negative promotion to physicians and objections/litigations before administrative and judicial authorities.

(164) According to two documents found in on-site inspection at NOVARTIS, NOVARTIS actively informs physicians that *Altuzan* is not suitable for use in ocular treatments. The main basis for NOVARTIS' negative promotional activities is this misleading information in *Altuzan*'s SPC/PIL. At this point, it should be noted that while promoting its own product, a pharmaceutical company's use of misleading information about a competitor's product and thus trying to ensure that the competitor's product is not preferred, is also controversial in terms of promotional legislation. In fact, the sixth paragraph of 6th article of Regulation on Promotional Activities of Medicinal Products for Human Use states that "Promotion cannot be done by giving misleading, exaggerated or unproven information that may unnecessarily encourage the use of the product or cause unexpected risky situations, or by using images that are interesting and not directly related to the product itself." Accordingly, it is clear that encouraging the use of *Lucentis* by presenting misleading information about *Altuzan* to physicians that are not suitable to academic studies and global practices is also not in accordance with the relevant legislation.

(165) At this point, it is beneficial to underline information in the written statement of SSI. The argument that the use of this drug in intraocular treatments leads to undesirable results (endophthalmitis) is highlighted in the negative promotion of *Altuzan*. However, in the response SSI sent, it was stated that there was no detection of adverse effects among 15,000 patients who received *Bevacizumab*, as claimed

(166) The decision of the Van 1st Administrative Court, numbered 2017/2179 E. and 2020/335 K., sent by the complainant, is remarkable in terms of the subject of investigation (Document-90). (.....) who developed endophthalmitis after intravitreal injection of *Ranibizumab* in Van Yuzuncu Yil University Ophthalmology Clinic, filed a lawsuit demanding compensation against the President of the University. Endophthalmitis was also observed in other patients who were administered injections on 21.12.2016, when (.....) who had been followed up with the diagnosis of diabetic retinopathy and macular degeneration was administered injection. With its decision dated 13.03.2020, the court decided that compensation to be paid to the plaintiff.

(167) The case which is the subject of the court decision shows that intraocular use of anti-VEGF agents always poses certain levels of risk and that this is not only valid for *Altuzan*, for example negative consequences may occur when *Ranibizumab* is used. However, while the parties to the investigation, relevant undertakings and associations frequently referred to the endophthalmitis case in Kırıkkale University Faculty of Medicine, the case which occurred after *Ranibizumab* injection and resulted in permanent vision loss was never mentioned. This is considered to be an extension of the strategy of disseminating misleading information to physicians, public institutions and the public opinion.

(168) Also, bearing the fact that *Lucentis* is a licensed product which was approved by TMMDA in mind, the SPC of this product will be referenced. Accordingly,

"*Intravitreal injections including those with LUCENTIS have been associated with endophthalmitis, intraocular inflammation, ruptured retinal detachment, retinal detachment and iatrogenic traumatic cataract."* Once again, in SPC, it was stated that increased intraocular pressure is very common in *Lucentis* use. It is known that this is also true for other anti-VEGF agents. Therefore, despite the large number of studies showing that there are no significant differences between anti-VEGFs in terms of efficacy and side effect profile, country practices and authority and court decisions that support/legalize these practices, it is clear that certain cases and findings that apply to all anti-VEGFs are systematically highlighted, that these are only attributed to *Altuzan* and that the perception of physicians, public institutions and public opinion are negatively affected.

(169) The strategy of NOVARTIS on the subject is also evident in its objections to SSI and TMMDA, and the lawsuits it filed against the amendment on HIC dated 28.12.2018. Again, one of the main pillars of NOVARTIS' arguments was this misleading information, which differed from the statement in the original reference document, that *Altuzan* is not suitable for intravitreal use. ROCHE, on the other hand, did not object to HIC amendment to relevant public institutions and did not go to court. Therefore, on the official objections front, ROCHE remained more passive compared to NOVARTIS. However, Association of Research-Based Pharmaceutical Companies (AIFD) has filed an objection/litigation against the HIC amendment. ROCHE is a member and represented by a member in the board of directors in AIFD, therefore AIFD represents its will and is expected to protect its interest. Thus, it is clear that the will of both parties to the investigation is reflected in the administrative and judicial processes.

(170) At this point, it should be noted that NOVARTIS is also a member of AIFD and has a representative on the board of directors. According to information obtained from AIFD, meetings and correspondences were held within the body/organization of the association prior to the objections to the HIC amendment and NOVARTIS also attended these events. Briefings of AIFD regarding the process were also conveyed to ROCHE and NOVARTIS directors. In this context, it is understood that the parties to the investigation were not only represented by AIFD during the objection/litigation process, but they also come together in events held within or through AIFD.

(171) According to the above-mentioned findings, ROCHE was active in licensing and NOVARTIS was active in negative promotion to physicians in the case under investigation. While NOVARTIS was the party to the investigation which directly objected to SSI and TMMDA and filed a lawsuit against HIC amendment, the will of ROCHE was also represented in AIFD's initiatives. Furthermore, the parties to the investigation attended/were involved together in many meetings and correspondence before AIFD. As a result of these finding, it is obvious that ROCHE and NOVARTIS acted in parallel in the case under investigation.

(172) Following the evaluation above, two striking observations were made. Firstly, in the process starting with the request of TMMDA to change *Altuzan's* SPC/PIL, it is understood that ROCHE's main undertaking was actively involved in the process and directed ROCHE to resist TMMDA's request. Accordingly, it is considered that the global strategy detected in the ICA and CJEU reviews is also valid for Turkey.

(173) On the other hand, the fact that a document (Document-8) containing trade secrets about *Lucentis*' marketing strategy was found during the on-site

inspection at ROCHE is noteworthy. The Excel file named “Lucentis Value Proposition Plan” includes *Lucentis’* marketing policy, what kind of brand perception it will create, the scope of the value proposition campaign it will launch in April 2019, what the success metrics of the campaign are, who has which roles on duty in the campaign, the contact information of these people, through which channel the target audience will be reached in marketing activities, which actions will be taken in which periods of 2019, the purpose of the brand and the messages it will give to consumers and physicians. The fact that this Excel file which contains details that may constitute trade secrets regarding a campaign belonging to *Lucentis* sold by NOVARTIS, was obtained during the on-site inspection at ROCHE strengthens the possibility that an agreement may exist between ROCHE and NOVARTIS in order to increase the sales of *Lucentis*, and it even raises the suspicion that while trying to prevent the use of *Altuzan,* which ROCHE is marketing in Turkey, in ocular diseases treatments, in the meantime it may be supporting the marketing campaign of *Lucentis.*

(174) The fact that such a document related to one of the products under investigation is found in the supplier of the rival product clearly shows that the parties are in communication about the investigation. Because it is clear that ROCHE cannot obtain such a document and the information it contains from known and public channels -without directly contacting NOVARTIS-. In addition, it is found that ROCHE and NOVARTIS came together regarding the case under investigation during the events held by/through AIFD. It is not possible to provide a reasonable explanation for this situation from the perspective of competition law.

(175) As a result, the fact that NOVARTIS and ROCHE discouraged the use of *Altuzan* by directing the administrative or judicial processes with misleading information by highlighting the endophthalmitis risk and side effects of *Altuzan* in a way that will shift the demand to *Lucentis* in intraocular treatments by acting in harmony, their efforts to create a perception that *Altuzan* and *Lucentis* are different which does not reflect the truth and in this context, making negative promotions about *Altuzan* to physicians are considered to be violating Article 4 of the Act No 4054.

I.4.2 Evaluation within the Scope of Article 5 of Act No. 4054

(176) According to the Guidelines on Horizontal Cooperation Agreements (Horizontal Guidelines), which determines the principles to be taken into account in the evaluation of agreements between undertakings, associations of undertakings and concerted practices which are in the nature of horizontal cooperation within the framework of Articles 4 and 5 of Act No. 4504, in case of an agreement between existing or potential competitors, cooperation is of a “horizontal nature”. In the market for intraocularly applied anti-VEGF molecules, since *Lucentis* which is sold by NOVARTIS in the Turkish market, and *Altuzan* which is sold by ROCHE, are considered to be substitutes for each other in accordance with academic studies, opinions of public institutions and organizations related to ophthalmologists and world practices, it is clear that the aforementioned undertakings are actual competitors in the relevant product market and therefore the cooperation agreement between them is of horizontal character.

(177) According to the Horizontal Guideline, the evaluation made within the framework of Articles 4 and 5 of the Act consists of two stages. The first stage is to assess whether the agreement between undertakings is restrictive of competition by object or has an actual or potential effect to restrict the competition within the scope of Article 4. If the agreement is found to be restrictive of competition within the scope

of Article 4, the second stage starts and at this stage, an exemption evaluation is made within the framework of Article 5, taking the competitive benefits and restrictive effects on competition that will arise as a result of the agreement into account.

(178) The evaluations that the horizontal cooperation agreement between ROCHE and NOVARTIS is within the scope of Article 4, and that it is restrictive of competition by object and by effect are mentioned above. As was mentioned in the Guidelines on the General Principles of Exemption (Exemption Guidelines), an agreement that unduly restricts competition because of its legal and economic characteristics and is unlikely to create economic benefits to outweigh its negative effects on competition will fail to meet the conditions for exemption. Limitations such as price-fixing between competitions, allocation of territories or customers are among these restrictions. It is considered that the agreement between ROCHE and NOVARTIS cooperating in the market of intraocularly applied anti-VEGF molecules in such a way to put *Lucentis* forward, limits the competition between the parties unduly.

(179) Besides, an agreement within the scope of Article 4 of Act No. 4054, can be exempted from the implementation of Article 4 only if all the conditions in Article 5 of the same Act are met. In the first paragraph of Article 5 of the Act, the exemption conditions are listed as follows:

"a) Ensuring new developments and improvements, or economic or technical development in the production or distribution of goods and in the provision of services,

b) Benefiting the consumer from the above-mentioned,

c) Not eliminating competition in a significant part of the relevant market,

d) Not limiting competition more than what is compulsory for achieving the goals set out in sub-paragraphs (a) and (b)."

(180) Since in the pharmaceutical industry, it is the patient who uses the drug and it is the physician who prescribes the drug and it is the state who is paying for the drug mostly, and *Altuzan* was not required to be used compulsorily in the first-line treatment until the HIC amendment dated 28.12.2018, taking into account that the use of the more affordable *Altuzan* by the physicians who are economically insensible was deterred by the joint effort of the parties and thus the health system had to endure a significant cost increase as a result of the efforts of the afore-mentioned undertakings; while no development or improvement can be mentioned in the market of intraocularly applied anti-VEGF molecules within the scope of subparagraph (a) of Article 5 of the Act No. 4054, it is seen that irreparable damages have arisen on the demand side, in general terms, before "consumers" within the scope of subparagraph (b) of the same article. For the reasons listed, it is considered that ROCHE and NOVARTIS cannot benefit from the exemption within the scope of Article 5 of the Act No. 4054.

I.4.3. Evaluation of Pleas

I.4.3.1. ROCHE's Plea and its Evaluation

I.4.3.1.1. The Plea related to Procedure

(181) **The following arguments were stated: It is stated that from the documents and information obtained during the on-site inspection, it is**

concluded that (I) ROCHE exhibits behaviors to narrow the usage areas for ophthalmic purposes of the product named *Altuzan* in its portfolio and (ii) ROCHE and NOVARTIS made attempts to discourage the use of *Altuzan* by ophthalmologists in the treatment of AMD, however, the documents and information on which those conclusions are based on are not disclosed, and that this situation violates ROCHE's right of defense; therefore, copies of the information and documents that form the basis of the aforementioned determinations were requested.

(182) The information and documents accepted as a basis for the findings in the Investigation Report were submitted to the parties as an attachment to the Report.

I.4.3.1.2. The Plea Regarding Principle

(183) **General Arguments**

The statements in the plea are as follows:

- **Within the scope of Vascular Endothelial Growth Factor (VEGF) research program which enables the discovery and development of the active substance *Bevacizumab,* GENENTECH found that the use of this molecule in the treatment of ocular diseases caused some problems, which led to the emergence of *Ranibizumab*, a specific anti-VEGF developed specifically for the field of ophthalmology, in parallel with development activities of *Bevacizumab* in the field of oncology.**

- **Two billion USD was invested to develop *Ranibizumab,* and GENENTECH would not work to develop *Ranibizumab* if *Bevacizumab* was suitable for ophthalmological use, and the two products are produced with different research and development procedures which result in completely different two molecules and carried out parallelly, the stages in question clearly show that *Lucentis* is not in any way a clone or part of *Avastin, Avastin's* development and licensing was completed years before *Lucentis,* and between the two products, it was *Avastin* which obtained a license first.**

- **The approved indications in *Avastin's* license are limited to the field of oncology, do not include any ophthalmological indications, after *Avastin's* introduction to the market, *Avastin* was widely used off-label in the ophthalmic field, patients undergoing oncology treatment and also suffering from AMD showed improvement in both conditions as a result of *Avastin* use, and *Avastin* was widely used off-label in the ophthalmic field due to the absence of a licensed drug used in the treatment of AMD, such off-label use of *Avastin* has led to significant regulatory controversy after *Lucentis'* licensing.**

(184) While there are differences between *Avastin* and *Lucentis* (such as molecule, molecular weight), such differences are not considered to be an obstacle for the said drug to exist in the same product market. While determining the relevant product market, however, scientific studies and authority decisions regarding whether the active substances are equivalent of each other in terms of ocular diseases treatment were reviewed and information obtained from physicians were evaluated in order to determine demand-side substitution. As a result, it is concluded that *Avastin* and *Lucentis* can be used as substitutes for each other. There are numerous scientific studies showing that *Bevacizumab* does not differ statistically on a significant level from *Ranibizumab* and *Aflibercept* in terms of efficiency and that they are also similar in terms of side effects. Detailed explanation regarding this subject is mentioned in

“Relevant Product Market” section.

The statements in the plea are as follows:

- **The competition authorities of 26 EU countries including those with deep-rooted competition policies such as Germany, England, Belgium, Netherlands, Sweden and Spain in the European Council or European Union have not made similar claims about Roche Group and/or relevant Roche subsidiary operating in the relevant countries or Novartis Group and/or relevant Novartis subsidiary operating in the relevant countries.**

- **The fact that vast majority of the EU member countries have not opened an investigation in their respective countries with similar claims as in France and Italy since 2014 and the fact that although European Commission made a request for information after the Italian and French processes appeared on media, no official investigation was opened shows that the claims made in Italy and France were based solely on local/country-specific reasons.**

- **To jointly handle a number of Italy-specific issues regarding the competition between *Avastin* and *Lucentis,* ICA claimed that the afore-mentioned subsidiaries are coordinating. This shows clearly that ICA investigation is specific to current market conditions and the behavior of Roche AG and Novartis AG’s subsidiaries in Italy**

- **ICA made an evaluation in the decision regarding this specific situation of Italy that Italy exhibited a special situation within EU especially regarding the extremely widespread use of *Avastin* in private clinics, and therefore whether the decision made by ICA can be a model should be considered. The act and processes which led to ICA’s said decision did not happen in our country, it is not possible to make claims similar to the ones made in Italy in Turkey against ROCHE.**

(185) The fact that other countries do not make similar claims about Roche AG and Novartis AG does not pose an obstacle for the Competition Authority to review a valid allegation for Turkey. The Competition Authority makes its assessments in a way that they are valid for the Turkish market.

(186) ICA decision, on the other hand is taken into consideration upon the determination of the fact that the afore-mentioned undertakings are carrying out the same strategy in some countries including Turkey. The existence of the violation was not determined based on this decision alone. The afore-mentioned decision is included in the product market section in brief together with other decisions by other authorities (United Kingdom, France, Spain) because it is taken in a subject similar to that of the investigation conducted in Turkey. However, the relevant product market definition was not based on ICA authority decision alone. The evaluations were within the scope of the file were made on the following facts: ROCHE and NOVARTIS act jointly and encourage the use of *Lucentis* among rival products in intraocular treatments and discourage preffering *Altuzan* and in order to achieve this, they are directing/trying to direct the administrative/judicial process with misleading information and making negative promotion of *Altuzan* to the physicians and it is concluded that the way the parties to the investigation act is similar to the case example examined in Italy. Detailed evaluation about the subject is given in the evaluation section.

Arguments that There are Differences Between Italy Investigation and

Turkey Investigation

The statements in the plea are as follows:

- **The claims of ICA are based specifically on a communication within the Novartis Group and some e-mail correspondence between Roche Italy and Novartis Italy employees.**

- **It was argued by the ICA that the cooperation strategy restrictive of competition was actually implemented by minimizing independent scientific studies concluding that *Avastin* and *Lucentis* had equivalent product value in the field of ophthalmology, and by making and disseminating news that would raise public concern about the safety of intravitreal use of *Avastin*.**

- **Compared to other countries, off-label use of *Altuzan* in Turkey is unique. Despite the fact that under the principles of OLDL Guidelines, there is specifically the ruling stating "Off-label drug use will not be allowed for diseases that can be treated with drugs within the approved indication and standard dose. However, the demand of the patient and physician is taken into consideration in the treatment options that provide a significant pharmacoeconomical advantage.", use of *Altuzan* is permitted continuously.**

- **OLDL in the OLDL Guidelines and its annexes has allowed the use of *Altuzan* since 2007 for eye-related diseases, it classifies it as pharmaeconomically advantageous treatment option, even though there are other drugs with licensed indications such as *Lucentis* in this field.**

- **ROCHE has not had any contact with TMMDA regarding the inclusion of *Altuzan* in OLDL or its inclusion in the list or the scope of the indications it is related to, since the information and documents at hand cannot prove the existence of such contact in this regard, ROCHE does not have any contact with NOVARTIS either in this respect.**

- **ROCHE did not resort to any legal procedure against OLDL or OLDL Guidelines either and the Italian Investigation and the conditions in Turkey are completely different due to those facts.**

- **In the historical development of off-label use of *Altuzan* in Turkey, ROCHE's approach (i) is not an initiative to restrict or terminate the off-label use of *Altuzan*, (ii) the situation is different in Turkey from Italy, which is the basis for the allegations under investigation, both in terms of regulatory structure and firm behavior regarding Altuzan's off-label use.**

(187) As stated above in the response given to the relevant plea, the Italy case was not accepted as the sole basis in the investigation which is the subject of the file. The evaluations made within the scope of the file are made on the fact that ROCHE and NOVARTIS acted jointly to encourage the use of *Lucentis*, one of the rival products, in intraocular treatments and discourage preferring *Altuzan*, and in order to achieve this, they were directing/trying to direct the administrative/judicial process with misleading information and making negative promotion of *Altuzan* to the physicians, and it was concluded that the parties to the investigation acted similarly to the case examined in Italy, in Turkey as well. Detailed information on the subject is in the evaluations section.

(188) In the evaluations made, it was clearly stated that ROCHE did not raise an objection to the relevant public institutions against the HIC amendments and did

not go to court, and it was concluded that ROCHE remained in a relatively passive position compared to NOVARTIS on the official objections front. However, AIFD has filed an objection/lawsuit against the HIC amendment. ROCHE is a member and represented by a member in the board of directors in AIFD, therefore AIFD represents its will and is expected to protect its interest. Therefore, it is clear that the will of both parties to the investigation is reflected in the applications made before the administration and judiciary. According to the information obtained from AIFD, meetings were held, and correspondences were made within the body/organization of the association before the objections to the HIC amendment and ROCHE and NOVARTIS attended these events. These briefings of AIFD about the process were delivered to the directors of ROCHE and NOVARTIS as well. Within this framework, the parties to the investigation were not only represented by AIFD, but also came together in events held within or through AIFD during the objection/litigation process. In this regard, in the case subject to the investigation, ROCHE was active in licensing while NOVARTIS was active in the promoting to the physicians. While it was NOVARTIS who directly objected to SSI and TMMDA and the party to the investigation filing a lawsuit against the HIC amendment, ROCHE's will was also represented in AIFD's initiatives. Furthermore, the parties to the investigation attended to/involved in a number of meetings and correspondences jointly before AIFD. As a result of these findings, it is not possible to say that ROCHE and NOVARTIS acted independently of each other during the case under investigation.

(189) The fact that a document containing trade secrets regarding *Lucentis*' marketing strategy was found during the on-site inspection at Roche also clearly shows that the parties are in communication regarding the investigation.

Arguments Related to the Allegations in the Investigation Statement

The statements in the plea are as follows:

- **ROCHE does not have any activities in the field of ophthalmology and does not have any human resources or budget in this field, and ROCHE has historically not taken an active approach in any discussion about *Altuzan/Lucentis* except for the changes that would significantly increase the possible legal responsibilities vis à vis the patients and HIC amendments at the end of 2018, and it has a duty limited to conveying the developments in the regulatory institutions only to TMMDA.**

- **ROCHE's senior managers do not have a clear instruction or approach about either off-label use or not to be a party to the legal considerations related to this issue.**

- **In fact, ROCHE has no interest in ophthalmology products. In addition, Roche's *Avastin*, CD20 and Lung & Skin Commercial Insight Analyst Hande Ataman stated in response to the aforementioned e-mail that she does not remember the name of the product (Eylea) whose indication contradicts with *Lucentis* and informed the relevant team about the fact that Eylea has been on the market since 2014, which showed that even Roche's senior staff has no idea about the ophthalmic market. Therefore, the allegations stating there is a relationship restrictive of competition in the ophthalmic market between *Altuzan* and *Lucentis* are baseless.**

(190) According to the above-mentioned evaluations, Roche did not object to the relevant public institutions and did not take legal action against the HIC

amendment and ROCHE remained relatively more passive in terms of official objections compared to NOVARTIS. Detailed explanations on the subject are given above.

(191) In the process starting with the TMMDA's request to change *Altuzan*'s SPC/PIL, it is clear that ROCHE's parent undertaking was actively involved in the process and directed ROCHE to resist TMMDA's request. Accordingly, it is considered that the global strategy detected in the evaluations of ICA and CJEU is also valid for Turkey. On the other hand, a document containing trade secrets about *Lucentis*' marketing strategy was found during the on-site inspection at ROCHE. The fact that such a document related to one of the products under investigation is found in the supplier of the rival product clearly shows that the parties are in communication about the investigation. In addition, it has been determined that ROCHE and NOVARTIS came together regarding the case under investigation at events held within/through AIFD. It is not possible to provide a reasonable explanation for this situation from the perspective of competition law.

The statements in the plea are as follows:

- **The amendments in SPC dated, The objections made to TMMDA by ROCHE regarding ROCHE's request to remove the phrase reflected on the SPC by TMMDA in parallel with the changes made before EMA, and which still remains valid and the claim that ROCHE made attempts to cancel the amendment as a result of the amendment made by SSI in the HIC regarding the reimbursement of *Altuzan* on 28.12.2018 cannot be interpreted as "Roche tries to narrow the areas of use for ophthalmic purposes of the product *Altuzan* in Roche's portfolio",**

- **According to the art. 8/n of the Regulation on Licensing of Medicinal Products for Human Use dated 19.01.2005 and numbered 25705, the documents to be submitted by the person wishing to obtain a license for a product shall include the SPC, patient information leaflet and packaging samples of the product which are guaranteed to be up to date by the applicant,**

- **In the continuation of the article, it is stated that "It is mandatory to notify the Ministry of the information that is updated among those listed in this article.", and according to art. 24/c of the said regulation, it is the responsibility of the license holder before the Ministry to update the short product information and the patient information leaflet, when necessary, in order to ensure the correct and safe use of the product,**

- **In accordance with the specified legislation, SPC and patient information leaflet of the original product must be prepared in line with the current documents abroad, following the updates, this is deemed mandatory by TMMDA,**

- **It is a very usual situation in the pharmaceutical industry to make the necessary updates in line with the current documents and there are many correspondences in which TMMDA requested information from ROCHE regarding the indications accepted in other countries, the content of the approved SPC at EMA and FDA,**

- **Within the framework of the aforementioned liabilities, ROCHE submitted its application to TMMDA on 29.12.2011, which resulted in the change of *Altuzan*'s SPC on 30.05.2014, and Roche's compliance with its legal**

obligations shall not be a subject of criticism within the framework of competition law,

- **The afore-mentioned applications made due to legal obligation cannot be against the law, and ROCHE's informing TMMDA is a one-sided procedure, and such a process cannot be a basis for cooperation allegations.**

(192) Although the expression in the original prospectus of the product is "*Altuzan is not formulated for intravitreal use.",* ROCHE has applied to TMMDA in 2011 to add the phrase "*Altuzan is not suitable for intravitreal use."* to *Altuzan*'s SPC and PIL. Later, after TMMDA stated that in these circumstances, the licenses of 100 mg and 400 mg forms of *Altuzan* could be suspended, TMMDA's request for correction of the relevant statement was fulfilled in 2019. The said different translation is considered to be a part of the strategy of disseminating misleading information about *Avastin/Altuzan.* Thus, this expression in SPC/PIL and other statements made in support of the said expression were used as a basis both for the negative promotions towards physicians and the objections/litigations before administrative and judicial authorities. In this context, not the application made due to a legal obligation, but the fact that ROCHE and NOVARTIS acted jointly and encouraged the use of *Lucentis* among rival products in intraocular treatments and discouraged preffering *Altuzan*, thus manipulating the administrative processes with misleading information is described as violation within the scope of Article 4 of the Act No. 4054.

The following statements in the plea:

- **There is no document regarding the allegation that Roche Turkey took initiatives to reverse the amendments made in HIC dated 28.12.2018, prioritizing the use of *Altuzan* for various ophthalmic circumstances,**

- **ROCHE was not the only party in the correspondences on the subject under the body of AIFD, but committee members of Bayer, Novartis, Allergan and external lawyers of AIFD are also a part of them. These correspondences will not constitute a violation, as AIFD, handled the issue as a sector representative and they are supported by occupational organizations such as TOA, which are significantly critical of amendments.**

- **If these correspondences constitute a violation, allegations must also be made against AIFD, TOA and other companies, on the other hand, ROCHE did not take any legal action against the amendment in HIC after the SSI rejected the correspondences of AIFD.**

(193) In the above-mentioned evaluations, it is stated that ROCHE did not object to the relevant public institutions against HIC amendment and did not take legal actions, it is concluded that Roche was in a relatively passive position compared to NOVARTIS with respect to the official objections. However, AIFD filed an objection/litigation against the HIC amendment. ROCHE is a member and represented by a member in the board of directors in AIFD; therefore, AIFD represents its will and is expected to protect its interests. As a result, the will of both parties is reflected in the applications made before the administration and the judiciary. According to the information obtained from AIFD, meetings and correspondences were held within the body/organization of the association prior to the objections made against HIC amendment, and ROCHE and NOVARTIS also attended these events. Briefing done by AIFD regarding the process was also delivered to the directors of ROCHE and NOVARTIS. In this framework, the parties to the investigation were not

only represented by AIFD during the appeal/litigation process, but also came together at events held within or through AIFD. In this context, ROCHE was active in licensing, and NOVARTIS was active on promotions to physicians in the case under investigation. While it was NOVARTIS, which is the party to the investigation that directly appealed to SSI and TMMDA and filed a lawsuit against the HIC amendment, the will of ROCHE was also represented in AIFD's initiatives. Furthermore, the parties to the investigation attended/ involved together in many meetings and correspondences before AIFD. As a result of these findings, it is not possible to state that ROCHE and NOVARTIS act independently of each other.

(194) Also, the fact that a document containing trade secrets regarding the marketing strategy of *Lucentis* were found during the on-site inspection at ROCHE clearly demonstrates that the parties are in communication regarding the investigation.

The statements in the plea are as follows:

- **Novartis AG is the other shareholder with (.....)% of Roche AG's shares with all related voting rights between 2001-2007, however, (.....)% of the company's capital consists of non-voting shares. Therefore the shares of Roche AG within Novartis AG represent (.....)% of the total voting rights of Roche AG and it does not have any control over Roche AG,**

- **There is no evidence that the afore-mentioned shares create mutual benefits, and the minority interest shareholding is common, and there is no hindrance to the continuation of this shareholding between companies in the future, unless there is concrete evidence that it restricted competition by effect,**

- **If Novartis AG's shareholding in Roche AG were a tool for mutual beneficial partnership of the two companies, this situation would constitute a very serious claim in EU Competition Law, and in this case, both ICA's and the European Commission's intervention would be expected in this structural problem, because accepting a behavioral solution would not be sufficient if a structural problem leads to an agreement on restricting competition. However, ICA, EU Commission or 27 EU member states do not question this shareholding relationship.**

(195) GENENTECH has transferred the marketing and sales rights of *Avastin* (*Altuzan)* containing *Bevacizumab* to ROCHE, and the same rights of *Lucentis* containing *Ranibizumab* to NOVARTIS, outside the USA. According to the License Agreement signed between GENENTECH and NOVARTIS, NOVARTIS, (.....) pays to GENENTECH and therefore, pays indirectly to ROCHE. In this context, it is possible to state that the legal and commercial relations between the parties to the investigation constitute the economic foundations of the global strategy which is also reflected in the Turkish market for medicine for human use, because ROCHE earns a significant amount of income from the sales of *Lucentis*, a rival of its own product, and furthermore, much higher priced one. This will reduce/perhaps destroy the incentive for ROCHE to actively evaluate the sales potential of *Altuzan*, which is widely preferred in the same treatment areas. Furthermore, it is obvious that the widespread use of *Lucentis*, which is a much higher priced product, instead of *Altuzan*, will increase the total sales in the relevant market.

Other Statements

(196) **The following statements in the plea: the cartel allegation is based**

on the claim that the parties are rivals in Turkey, that there is no relation between the compulsory substitution relationship established with the HIC amendment and the products being rivals, 14 hospitals whose opinions were consulted reported that they never or rarely used *Altuzan* mainly in intraocular treatments and TOA gave the same response; however, the report argues that,, the relevant products are in the same market based on the fact that *Altuzan* is used in other countries.

(197) The parties did not become rivals in 2019, when the HIC amendment entered into force. In economic terms, competition means that two products can be used as substitutes for each other. Therefore, whether the two products are competitors is not determined according to public regulations but by means of evaluating supply substitution and potential competition, especially demand substitution. Especially when considered in terms of demand substitution, it is seen that both *Avastin* in global markets and *Altuzan* in Turkey are frequently used off-label in relevant treatments.

(198) As stated above, it was found that private hospitals, which were consulted within the scope of the investigation, used *Altuzan* in significant amounts in relevant treatments before the HIC amendment. For instance, in the private hospitals which were consulted during the investigation, the rate of *Altuzan* usage before the HIC amendment varied between 60% and 90%.

(199) In the responses of the public hospitals evaluated by ROCHE as favorable, no significant difference was stated between *Altuzan* and other anti-VEGF agents in terms of efficacy and safety. The usage patterns and application doses of the drugs in question did not change depending on the stages or types of the diseases, while the frequency of usage could vary. Thus, it was not possible to agree with the objection of the party.

(200) **The following arguments in the plea: in the "Relevant Market" section, academic studies are cited without researching and reading. A study that does not reflect the opinion of the EU Commission is presented as a Commission Report. Biased references are made, and these references are not presented truly, quotations are made without referencing the source and that the summaries of the ICA decision are based on the publications of third parties and their subjective evaluations and that even the paragraph numbers referred to in the ICA decision in the Investigation Report are the same.**

(201) "Study on the Off-Label Use of Medicinal Products" referred to in 131-138th paragraphs of the Investigation Report was published in February 2017 at www.ec.europa.eu, the official website of the European Commission. The Commission has experts make various studies and prepare reports in the fields requiring expertise. Although there is an annotation on the second page of the said study that the opinions mentioned in the study may not reflect the knowledge and views of the Commission, this will not change the fact that the study was published on the Commission's website. In addition, as seen on the Commission's website, the corporate author of the said study is The European Commission's Directorate-General for Health and Food Safety[75]. Also, the personal authors of the study mentioned in the Investigation Report are as follows: Marjolein Weda, Joëlle Hoebert

[75] https://op.europa.eu/en/publication-detail/-/publication/ecf85518-d376-11e9-b4bf-01aa75ed71a1, Accessed: 11.09.2020.

Marcia, Vervloet Carolina, Moltó Puigmarti, Nikky Damen, Sascha Marchange, Joris Langedijk, John Lisman and Liset van Dijk. It was not their views that were cited but the concrete information about various country practices they obtained as a result of their studies. Therefore, it is not important at this point whether the afore-mentioned study reflects the views of the Commission or not. In addition, it is seen that there was not a concrete objection to the concrete information in the plea of the undertaking, and the only focus was on the fact that the study did not reflect the knowledge and views of the Commission.

(202) In the plea of the undertaking, it is claimed that there was a biased reference in paragraph 135 of the Investigation Report and these references were not truly. The afore-mentioned paragraph is as follows:

"*Therefore, whether the cost of Lucentis would be paid by the health system or not has been a topic of discussion. Roche AG tried to prevent the off-label use of Avastin with an emphasis on the safety risks when it is used off-label[76], but did not compare the efficacy of Lucentis and Avastin directly."*

(203) In the afore-mentioned paragraph, a footnote contains a reference to the source from which the information was obtained. The said information is also in the study titled Study on the Off-Label Use of Medicinal Products in the European Union. It is not possible to accept that detailed examination of the case subject and referencing to the information and documents compiled on the subject within the scope of the investigation is biased and grave as claimed by the undertaking.

(204) The claim that quotations were made without citing the source is in the paragraph 140. Paragraph 140 of the Investigation Report is as follows:

"*The fact that ICA's definition of the relevant product market is based on the demand-side substitution relationship has been criticized by some circles[77]. The basis of the criticism is that the demand for Avastin in the treatment of eye diseases in Italy is not a direct preference of doctors, Avastin is used off-label for economic reasons by doctors and this is against EU legislation. According to EU legislation, the off-label use of a drug is very limited[78] and pharmaceutical companies are expressly prohibited from promoting the off-label use of a drug[79]. However, the relevant legislation does not justify the fact that the parties shifted the request to Lucentis by spreading misinformation among doctors, public institutions and the public, raising concerns about Avastin's risks."*

(205) In the afore-mentioned paragraph, two footnotes refer to the relevant sources, and one footnote is used to explain an issue that does not need to be in the Investigation Report.

(206) The claim that the summaries of the ICA decisions are based on the publications of third parties and their subjective evaluations is also unfounded. The

---

[76] Health Canada Endorsed Important Safety Information on Avastin (Bevacizumab). Retrieved on March 2016 from http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14494a-eng.php.

[77] Killick J ve Pascal B (2015), Pharmaceutical Sector: Can Non-Authorised Products be Included in the Relevant Market for the Assessment of Alleged Anticompetitive Conduct? A Short Analysis of the Recent Italian Avastin-Lucentis Decision.

[78] A drug can be used off-label in approved clinical studies or in exceptional cases specified in Directive 2001/83 or Regulation 726/2004.

[79] Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to the medicinal products for human use, OJ (2001) L 311/67, Arts 86 and 87.

identities of the third parties, who are stated to have subjective views are unclear. In the Investigation Report, which does not need to have an academic nature in its essence, due to the technical dimensions of the subject, the diversity and quality of academic studies and the principles of academic citation are given maximum attention.

(207) **Claims classified as horizontal/concerted practice/cartel in the report's professional index are specified as agreement this time in the paragraph 180 of the report. Despite the cartel claim, none of the elements of the cartel definition in article 3 of the Regulation on Active Cooperation for the Detecting Cartels are shown. The report does not have a single piece of evidence of a joint will, contact or communication between ROCHE and NOVARTIS. The SPC amendment application dated 29.11.2011, which is said to be the starting point of the violation, is a unilateral transaction of ROCHE and is in no way related to NOVARTIS. The contact of the parties was not shown in terms of the process that started with the request of TMMDA for the change of SPC dated 05.11.2018**

(208) There was a reference to the explanations in the Horizontal Guidelines in the paragraph 178 of the Investigation Report. As stated in the third footnote of the Guidelines, the concept of "agreement" is used in the Guidelines to include the decisions of associations of undertaking and concerted practices. The term agreement in paragraph 180 of the Investigation Report is used in this sense. On the other hand, it should be noted that the subject of the investigation carried out within the scope of the file is concerted practice between the parties.

(209) In order to regulate the procedures and principles regarding the administrative fine in accordance with Article 16 of the Act no 4054 to be given to those who perform the prohibited acts in Articles 4 and 6 of the same Act, "Regulation on Fines to Apply in Cases of Agreements, Concerted Practices and Decisions Limiting Competition, and Abuse of Dominant Position" (Regulation on Fines) was issued. Accordingly, the basic fine is determined according to Article 5 of the Penal Code, and then the aggravating and mitigating factors are considered according to Articles 6 and 7.

(210) In order to determine the basic fine, whether the violation would be qualified as a cartel or not must first be evaluated. In Article 3 (d) of the Regulation on Fines, a cartel is defined as *"competition restrictive agreements and/or concerted practices between competitors for fixing prices; allocation of customers, providers territories or trade channels; restricting the amount of supply or imposing quotes and bid rigging."*

(211) With the violation in question, the undertakings who are parties to the investigation have aimed to shift the demand in the market of "intraocularly applied anti-VEGF molecules" to *Lucentis* by acting jointly, by disseminating misinformation to various public institutions and organizations, physicians, and associations of undertakings in order to raise concerns about the use of *Altuzan.* Considering this aspect, it is seen that selling *Lucentis* to patients who need intraocularly applied anti-VEGF molecules in their treatment will serve the common interests of the parties. On the other hand, it is understood that prescribing *Altuzan*, which is much more affordable than *Lucentis*, does not serve the common interest of the parties. Therefore, the sales of *Altuzan* were attempted to be suppressed by the joint will of the parties and the use of *Altuzan* as an intraocularly applied anti-VEGF molecule

was discouraged. In other words, the market of intraocularly applied anti-VEGF molecules is left to NOVARTIS with the joint will of the parties for the common interest of the parties. Thus, there was an attempt to use *Altuzan* only in oncological treatments and to keep it out of the *Lucentis'* market.

(212) This market-sharing by the parties to meet the demand for intraocularly applied anti-VEGF molecules with higher-priced *Lucentis* increases public spending without improving treatment or increasing efficacy. On the other hand, it is also disadvantageous for patients who are ultimate consumers, as physicians who are concerned about *Altuzan*'s risks direct their patients to get *Lucentis*, which is provided by the patient share, instead of *Altuzan* which is currently exempt from the patient share.

(213) In this context, following evaluations were made: The act under investigation comply with the allocation of a product market example, and in this respect, restricts competition. In addition, due to the attempt of shifting the demand for intraocularly applied anti-VEGF molecules to *Lucentis*, customers who were essentially buyers of these molecules shifted to *Lucentis*. The public institutions and organizations as well as that create the demand physicians were misinformed about *Altuzan*, and as a result, the intraocularly applied anti-VEGF molecules market and therefore indirectly the customers in this market were shared. As a result, this reduces the options for consumers and the public and causes financial damages. Therefore, the afore-mentioned actions are in line with the definition of cartel in subparagraph (d) of Article 3 of the Regulation on Fines and benefitting from the exemption under Article 5 of the Act No. 4054 is not possible.

(214) **The following statements in the plea: The Investigation Report accused ROCHE of not obtaining additional indication approval for *Altuzan*, not obtaining a license for a product in smaller form to be used for the eye, as well as not investing millions of dollars in a commercial area in which it did not want to be active at all and did not have any employees in sales and marketing, yet in the conclusion section of the report, there is no claim for not applying for *Altuzan* to be licensed in the ophthalmic field.**

(215) The objection stated in the plea does not reflect the truth. What the Investigation Report considers regarding Roche is the fact that the sales potential in an area other than cancer treatments was not evaluated rather than the fact that Altuzan is not receiving new indications. ROCHE's reluctance to meet the demand in the ophthalmology field and even its stance against it with its discourse and act is not understandable, given the following facts: scientific studies show that there is no significant difference between *Altuzan* and other anti-VEGF agents, the oldest drug used in relevant treatments in the world and in Turkey is *Altuzan/Avastin*, and *Altuzan/Avastin* is still highly preferred in this field in many countries, and in Turkey, *Altuzan* was first included in OLDL in Turkey in terms of these treatments and is still on this list, and this potential has become evident after the HIC amendment dated 28.12.2018 and the subsequent SPC amendment. Also, it is not necessary to obtain an additional indication for *Altuzan* in order to commercialize the said potential. For it is possible to use *Altuzan* in relevant treatments for a long time. Private hospitals, whose opinions were consulted during the investigation phase, stated that they preferred *Altuzan* mostly before the HIC amendment in the relevant treatments.

(216) An indication for intraocular applications and the development of a disposable form of the product are listed in the Investigation Report, among the acts

that can be expected from a pharmaceutical company that is at the point of commercially evaluating such potential. While public institutions encourage the use of *Altuzan,* which is similar to other products and costs less compared to these products, it is not difficult to foresee that the relevant processes will run faster and more smoothly than usual. However, at this point, even without the need for ROCHE to enter a new commercial area and invest "millions of dollars", it is possible for *Altuzan* to be used in the treatments of ocular diseases.

(217) **The following statements in the plea: The decision of the ICA which is often referred to in the evaluations was not examined. From the explanations about the duration of the violation, it was understood that the investigation report tried to draw a parallel with the file and the ICA examination, but this connection was not revealed. The ICA inspection was initiated upon the applications of the Italian Ophthalmological Society and Private Hospitals Association, after *Avastin*, which was in OLDL continuously since 2007, was removed from the reimbursement list in 2012. However, in the investigation report, the fact that *Altuzan* has been included in OLDL since 2007 in Turkey and is therefore within the scope of reimbursement is not considered significant. ICA mentioned situations specific to Italy, for instance, *Lucentis* has a market share of 78% for AMD treatment in all EU countries, while the same share was 43% in Italy. Furthermore, *Avastin/Altuzan* is repackaged in small sizes in Italy and is ready to use ocularly. Therefore, for physicians, there is no risk of dividing the product and no concern that may arise from it. However, there are no such practices in Turkey. The decision evaluating Italy-specific conditions does not point to a global strategy. There are plenty of correspondences pointing out the contact between the parties in the ICA decision. The elements referred to in this decision (such as the correspondences between General Directors, documents demonstrating cooperation between the parties) were not found in the investigation file.**

(218) The evaluations made within the scope of the file are applicable for the Turkish market. The existence of the violation was not detected based on this decision alone. In this sense, the ICA decision included together with the decisions of the authorities of other countries (United Kingdom, France, Spain), since the ICA decision is an authority decision made on a subject similar to the investigation carried out in Turkey. Still, the other determinations in the ICA decision were not considered directly applicable to Turkey, thus the factors specific to Turkey were examined in detail.

(219) Furthermore, the French Competition Authority made a press announcement on its official website on 09.09.2020. The announcement stated that NOVARTIS, ROCHE, and GENENTECH were fined a total of 444 million Euros on the grounds that they abused their dominant position in order to continue their sales of *Lucentis* against *Avastin* in ophthalmology field[80].

(220) In this context, although it is claimed that there is no document indicating cooperation between the parties, there are many documents in the investigation report. For example, during the on-site inspection at ROCHE, a document (Document-8) containing trade secrets regarding the marketing strategy of *Lucentis* was found. The fact that the supplier of the competitor product kept such a document about the products under investigation clearly shows that the parties are in communication

[80] https://www.autoritedelaconcurrence.fr/en/press-release/treatment-amd-autorite-fines-3-laboratories-abusive-practices, Accessed: 15.09.2020.

about the investigation because it is clear that ROCHE cannot obtain such a document and the information contained therein through common and public channels. In addition, it is found that in the events held within/through AIFD, ROCHE and NOVARTIS came together regarding the case that is the subject of the investigation. It is not possible to provide a reasonable explanation for this situation from the perspective of competition law. In Van Yüzüncü Yıl University Ophthalmology Clinic, a patient who developed endophthalmitis after intravitreal injection of *Ranibizumab* filed a lawsuit demanding compensation. The case that is the subject of the court decision shows that the intraocular use of anti-VEGF agents always involves certain levels of risk and that this is not only valid for *Altuzan*, for example, negative consequences may occur with the use of *Ranibizumab*. However, while the endophthalmitis case in Kırıkkale University Faculty of Medicine was frequently referred to by the parties to the investigation, relevant undertakings and associations, the case that occurred after the injection of *Ranibizumab* in Van which resulted in permanent vision loss was never mentioned. This is considered an extension of the strategy of disseminating misinformation to physicians, public institutions, and the public. In the case under investigation, ROCHE was active in licensing and NOVARTIS was active in negative promotion to the physicians. While NOVARTIS is the party to the investigation that directly filed a lawsuit against the HIC amendment, ROCHE's will was also represented in the AIFD's initiatives. Furthermore, the parties to the investigation attended/ involved together in many meetings and correspondences before AIFD. As a result of these findings, it is obvious that ROCHE and NOVARTIS acted parallelly in the case under investigation. The detailed explanations and documents on the subject are above and, it is clear that the Turkey-specific situations are examined within the scope of the investigation.

(221) **The following statements in the plea: the parent undertaking of ROCHE actively involved in the process and directed ROCHE to resist TMMDA's request. Accordingly, it was concluded that the decided global strategy in ICA and Court of Justice of the European Union (CJEU) examinations were still valid in Turkey. However, in the relevant correspondence of TMMDA, TMMDA requested that the EMA SPC be added to the responses of the pharmaceutical companies, and it is natural for ROCHE to seek the opinion of its parent undertaking in the process that started with TMMDA's letter dated 05.11.2018. There is no single correspondence in the report between ROCHE and its parent undertaking regarding the ophthalmic use of *Altuzan* and its impact on *Lucentis* sales.**

(222) In the documents above and obtained during the on-site inspections carried requested an objection to TMMDA's request. In addition, the response letter dated 27.03.2020 and numbered 3021 sent by ROCHE to the Authority is summarized above. ROCHE's correspondence with the Ministry of Health regarding the intravitreal use of *Altuzan* is in this response letter. In the afore-mentioned correspondence, the declaration letter sent from ROCHE's global headquarters to the Turkish headquarters was mentioned. In this letter, there is an emphasis on the fact that the statement "*Altuzan is not suitable for intravitreal use."* <u>*should not be removed*</u> from *Altuzan*'s product information.

(223) The fact that ROCHE is in contact with its parent undertaking (with global headquarters) regarding the SPC amendment is not what is considered significant within the scope of the file. However, relevant correspondences show that ROCHE's objection to TMMDA's requests was decided in line with the will of its parent

undertaking. Consequently, the file naturally includes the finding that the will regarding the SPC amendment pillar of the concerted practice, which is anticompetitive and therefore within the scope of article 4 of the Act no 4054, is determined at a global level.

(224) **The following statements in the plea: In the CJEU decision, which is used as a reference without being examined in the Investigation Report, it is stated that it is not the duty of the competition authorities to evaluate whether the drug sales are realized in accordance with the EU rules. It is illegal to claim in the Investigation Report that a statement approved by TMMDA in *Altuzan*'s SPC is misleading. Even if there was misleading information, it should be shown that it was realized jointly by the parties and that the demand for *Altuzan* increased after this phrase was removed. While all hospitals emphasize that *Altuzan* is not indicated in ophthalmic field, it is not possible to state that there is a dissemination of misinformation strategy based on the statement that this drug is not suitable for intravitreal use in the SPC. The report did not explain how the change in SPC in 2014 affected the off-label use of *Altuzan*. There is no data on the intravitreal use of this product, besides considering *Altuzan* and *Lucentis* sales, *Altuzan* sales grew rapidly in 2011-2014 period when the relevant phrase was not in the SPC, and this continued after the 2014 amendment. In addition, *Lucentis* sales were always on the rise before and after the SPC amendment, however, this is not shown in the report.**

(225) There is no evaluation that can be perceived to be referring to the CJEU decision as summarized above in the assessments made within the scope of the file. Discouraging the use of *Altuzan*, one of intraocularly applied anti-VEGFs, and promoting the sales of *Lucentis*, a competitor product in this field, changing SPC/PIL for this purpose, and strategic actions about informing public institutions and physicians are the subjects of the examination. No aspect of the investigation is related to the discretion regarding whether undertakings act in accordance with the legislation on medicine for human use. No claim or statement that can be interpreted as such are made that this discretion power belongs to the Competition Authority.

(226) The phrase stating *Altuzan* is not suitable for intravitreal use was included in the SPC after ROCHE's application dated 29.11.2011 and maintained its existence until 2019 when the TMMDA's request was made. This fact that this phrase was approved by the relevant Commission and finally by TMMDA and that TMMDA did not object to this phrase in similar processes, does not change the truth that there is no phrase that can be interpreted in this way in the original reference documents. Furthermore, the books and articles as well as the practices around the world and in Turkey also contradict with the statement on *Altuzan*'s not being suitable for said practices. In this sense, it was not possible to agree with the argument made by the party referring to the administrative process and why the phrase contains misleading information will be examined in detail below.

(227) ROCHE made the first application to TMMDA on 29.12.2011 for the change of SPC/PIL, including the addition of the statement that *Altuzan* is not suitable for intravitreal use. According to the findings within the scope of the file, it was concluded that the violation started with this development. Information and documents on this process obtained from ROCHE are in the file. In all correspondences and promotional activities about *Altuzan* not being suitable for intraocular treatments, this statement in SPC/PIL is a fundamental starting point.

(228) As summarized above, it was stated in the plea that the phrase in *Altuzan*'s SPC that the product is not suitable for intravitreal use was given too much importance and it was not determinant for physicians and hospitals who did not prefer *Altuzan*. However, in the opinion dated 26.01.2019 submitted by TOA to AIFD, this statement in Altuzan's prospectus was underlined, emphasizing the potential risks of intraocular use beyond being an off-label drug.

(229) In order to illustrate the impact of the 2014 SPC amendment on *Altuzan* and *Lucentis*' sales, a chart that consists of IQVIA "retail and hospital" data is included in the plea. First of all, it must be noted that since the relevant amendment was approved on 30.05.2014, that is even before the first half of 2014 was not over, it is not convenient to make the comparison between 2011-2014 period and 2015. Also, although it is known that the 100 ml form of *Altuzan* is preferred for intraocular applications, it would be misleading to look at the total sales of both forms of *Altuzan*. In the evaluation made within the scope of the investigation, an impact analysis was made on SUT amendment and a jump in *Altuzan'*s sales caused by the said change is demonstrated.

(230) **The following statements in the plea: Even though the application dated 29.11.2011 created an effect restrictive of competition, the old SPC was still valid from this application until 30.05.2014. In this case, the effect in question cannot be brought up until 2014. As a matter of fact, the Authority examined the data and meeting information as of 2016 instead of the data and meeting information dated 29.11.2011.**

(231) Even though the application dated 29.11.2011 was approved on 30.05.2014, it was the starting point of the concerted practice. The concerted practice consisted of the following: deterring the use of *Altuzan* by directing the administrative or judicial process with misleading information by highlighting the risk of endophthalmitis and side effects of *Altuzan*, in a way that will shift the demand to *Lucentis* in intraocular treatments, trying to create a perception that *Altuzan* and *Lucentis* are different, which is not true and promoting *Altuzan* negatively to the physicians in this context.

(232) The claim that the findings within the scope of the file are from the period after 2016 does not reflect the truth. The information and documents related to the process about the SPC amendment application dated 29.11.2011 were examined in detail. The oldest document related to the subject in on-site inspections is from 2015.

(233) **The following statements in the plea: Even though the first application for the inclusion of the relevant phrase in *Altuzan*'s SPC was made on 29.12.2011 and this application was finalized before TMMDA after 3.5 years, the TMMDA's request dated 05.11.2018 was fulfilled within 119 days. The process after ROCHE, who was accused of resisting TMMDA's request for a long time, made the amendment on 15.03.2019, was completed on 01.10.2019 after 6.5 months. Therefore, it is not legitimate to present the accusation towards ROCHE and present this as though it took about a year. During this process, ROCHE's notification to TMMDA that it did not participate in the SPC amendment, that is, exercising its constitutional right to petition, is also considered a violation. The amendment made in 15.03.2019 was approved on 10.05.2019. However, new changes on SPC and PIL were requested on 02.07.2019. These amendments ROCHE conveyed on 31.07.2019 were approved on 01.10.2019. Although it was stated in the report that the process was**

concluded on 10.05.2019, it was actually on 01.10.2019.

(234) As mentioned above, the statement that Altuzan is not suitable for intravitreal use is misleading. It is clear that this statement has no equivalent in the original reference documents on 29.12.2011 and 05.11.2018. The statement of the parent undertaking, whose opinion was sought in the process that started in 2018, clearly supports this detection.

(235) In the documents above and obtained during the on-site investigations carried out within the scope of the investigation, it is clear that ROCHE's global headquarters demanded an objection to the TITCK request. In addition, the reply letter dated 27.03.2020 and numbered 3021 (Document-29) sent to the Authority by ROCHE is summarized above. In this reply, the correspondence of ROCHE with the Ministry of Health regarding the intravitreal use of *Altuzan* is included. In the said correspondence, the declaration letter sent from the global headquarters of ROCHE to the Turkish headquarters was mentioned. In this letter, there is an emphasis on the statement in Altuzan's product information *"Altuzan is not suitable for intravitreal use."* not be removed.

(236) In this case, ROCHE objected to TMMDA's request and requested an extension of time for responding. Therefore, it is seen that TMMDA's request was not fulfilled "quickly".

(237) At this point, it is not true that "objection to the management's request" alone is considered a violation. As stated, the act considered to be within the scope of violation is trying to maintain the existence of misleading information in SPC that initiates the will for concerted action and serves for negative promotions. In other words, ROCHE's objection to the regulations made by public institutions and organizations in a way that will result in favor of both the public and ROCHE, in line with its common interests with NOVARTIS, and attempt to mislead the public in a way that will shift the demand to Lucentis for the treatment of relevant diseases are practices that are under the scope of the violation.

(238) As will be stated under the title of "I.4.4.3. Duration of Violation", the violation started with the application made on 29.12.2011 for the SPC amendment. A statement was added to Altuzan's SPC that the drug was not suitable for intravitreal use, which did not exist in the original reference documents. TMMDA's request dated 05.11.2018 was fulfilled by ROCHE on 15.03.2019. This amendment was approved by TMMDA on 10.05.2019. Within the scope of the investigation, the process was completed on 10.05.2019 regarding "the correction of the phrase that serves as the strategy for spreading false information". After TMMDA's request to remove all explanations related to intravitreal use from the SPC and PIL of the product, it is stated that these amendments were also made and approved on 01.10.2019.

(239) The effect of the violation was largely eliminated with the SUT amendment dated 28.12.2018 and at this point, it is legal to take as a reference the date, 15.03.2019, when the violation ended with the withdrawal of the investigation party from the concerted action.

(240) The process, which started with TMMDA's letter dated 05.11.2018, with the request to remove the phrase in Altuzan's SPC and PIL stating that this drug is not suitable for intravitreal use, was finalized with the approval by TMMDA on 10.05.2019 to change this statement like in the original reference document and to remove other relevant statements. In this context, the actual date for the termination

of the violation is not the termination of the TMMDA process, but the date ROCHE applied for the amendment. In this sense, since the will of the party is taken as the basis, the fact that the process is finalized at a later date is not seen as an issue that will change the conclusion. As a matter of fact, the administrative process took time to conclude in terms of licensing.

(241) **The following statements in the plea: The incorrect allegations against ROCHE were significantly influenced by two documents sent to the Authority by TMMDA, which contained information that did not comply with formal processes. This error should be corrected by holding a meeting with the Authority where TMMDA and ROCHE officials are present. The following explanations do not correspond to the formal phases in the section of the document no.91 sent by TMMDA to the Authority on the lawsuit filed by Bayer: "it was found that an expression non-existent in Altuzan's international SPC is found in the Turkish SPC. When the SPC regulation of the drug was made, the relevant expression in the EMA SPC was inadvertently written in the Turkish SPC wrong, and this part was completely removed with the decision dated 11.10.2018 upon realization of this error. It was stated that a letter was sent to ROCHE to make the necessary alterations within a month." First of all, the SPC amendment dated 11.10.2018 started with ROCHE's request. TMMDA did not take any actions as explained above and did not send any letters to ROCHE in this context. Within the framework of the decision dated 11.10.2018, it is not possible to completely remove the relevant phrases from the SPC, and the statement that Altuzan is not suitable for intravitreal use continued to appear in the SPC. Also, according to the document no. 91, the relevant information was removed from the SPC information published by the FDA in 2014 and it was stated that the company did not make the amendment it was obliged to before the practice dated 28.12.2018. However, there is no change requested by TMMDA and not fulfilled by ROCHE. These statements created the impression that ROCHE deliberately did not fulfill TMMDA's requests and caused ROCHE to be accused of misleading TMMDA in the Investigation Report. In the section of the document no. 91 sent by TMMDA to the Authority regarding the lawsuit filed by TOA, it is stated that the paragraph with a translation error in Altuzan's SPC was removed and it was corrected as in the original statement at the beginning of February 2019. This information also does not accurately reflect the formal phases.**

(242) As mentioned above, in the section where the information and documents relevant to the lawsuit filed by BAYER and TOA, which are obtained from TMMDA are summarized, the statements in the plea that are said to be incorrect are not included. Therefore, it cannot be claimed that mistakes were made due to the explanations that were not conveyed to the evaluations made within the scope of the file while summarizing the file.

(243) The reason for the evaluation as to why the violation ended on 15.03.2019 is given above.

(244) **The following statements in the plea: The sections of the Investigation Report that evaluated ROCHE's first written plea state that ROCHE's original prospectus had the "… is not formulated." expression, it is also stated that ROCHE applied to TMMDA for the addition of "… is not suitable." expression to Altuzan's SPC and PIL in 2014. In the section on the**

duration of the violation, it is stated that the process started with TMMDA's request dated 05.11.2018 and ended with the approval of TMMDA on the amendment of this statement as in the original reference document and the removal of other relevant statements on 10.05.2019. The report created the impression that an incorrect statement was corrected in 2019, but the letter dated 05.11.2018 did not state that the relevant expression was incorrect. Also, the 2019 amendment is not related to that matter but rather related to the removal of all statements regarding the intravitreal use of Altuzan. Furthermore, the process was concluded on 01.10.2019, not on 10.05.2019. Although the report creates the impression that the statement "… is not formulated" was corrected and preserved, there is no longer a single statement on intravitreal use in Altuzan's SPC and PIL. These statements were removed at TMMDA's request. Altuzan's PIL, which was never mentioned in the report, states that Avastin was developed for the treatment of cancer by intravenous injection. It was not developed or prepared for intraocular injection. It is not approved for use in such a way and it lists the side effects that may occur because of this. This phrase is later reflected in the PIL of the product. It cannot be argued that a product developed as such is suitable for intravitreal use.

(245) In paragraph 218 of the report, it is written inadvertently that ROCHE made the relevant SPC amendment application in 2014.

(246) The Investigation Report includes the expression *"The application that resulted in the approval of TMMDA dated 10.05.2019 was made by ROCHE on 15.03.2019. Therefore, it can be accepted that the will of the party in this area of the violation ends on the specified date."* In this context, the actual date for the termination of the violation is not the termination of the TMMDA process, but the application date of ROCHE for the amendment. Since the will of the party is taken as the basis, the fact that the process ends at a later date is not seen as an issue that will change the evaluation.

(247) The process, which started with TMMDA's letter dated 05.11.2018 regarding the request to remove the phrase that this drug is not suitable for intravitreal use in Altuzan's SPC and PIL ended with TMMDA's approval of the amendment of this statement as in the original reference document dated 10.05.2019.

(248) The fact that Altuzan is not formulated for intravitreal use and that it is not suitable for this certainly does not mean the same thing. As a matter of fact, in the original documents referenced in the Investigation Report and ROCHE's second written plea, it was stated that Altuzan was developed for the treatment of cancer and was not formulated for intraocular applications. However, there was not a warning in none of the documents that Altuzan was not suitable for the specified uses. In Turkey, Altuzan has been on OLDL "continuously" since 2007, that is, the drug has been registered by the Ministry of Health to be suitable for use in relevant treatments and as stated in its plea, ROCHE did not have any objections or actions against it. It is impossible to accept that the statement that a drug which has been used in intraocular treatments for years and significantly preferred by some hospitals even before the HIC amendment is not suitable for such applications is quite natural.

(249) **The following statements in the plea: No responsibility can be attributed to ROCHE for NOVARTIS' promotional activities of which ROCHE is unaware. It is not possible for ROCHE to promote in the ophthalmology field according to the legislation. However, it is necessary to present the evidence**

that ROCHE contacted physicians in this regard, if such evidence exists. There was not any evidence indicating that NOVARTIS' promotions were agreed and made jointly with ROCHE, and it was not explained which of these promotions and which content of these promotions were misleading and for what reason. The 14 hospitals replied that ROCHE did not organize any activities that discouraged the use of Altuzan.

(250) In the evaluations made within the scope of the file, it was stated that ROCHE was active in licensing and NOVARTIS was active in negative promotions to physicians. It is stated that NOVARTIS is the party of investigation that directly appealed to the SSI and TMMDA, filing a lawsuit against the HIC amendment, and that AIFD's initiatives also represented ROCHE's will. It was also stated that the parties to the investigation attended many meetings and correspondences together before the AIFD. When all of these findings are evaluated together, it is concluded that ROCHE and NOVARTIS acted in parallel in the case under investigation. As a result, ROCHE was accused of violation not because of negative promotions to physicians, but because it acted in parallel with NOVARTIS.

(251) ROCHE made the first application to TMMDA on 29.12.2011 for the amendment of SPC/PIL, including the addition of the statement that Altuzan is not suitable for intravitreal use. Within the scope of the file, it is concluded that the violation started with this. Information and documents obtained from ROCHE regarding this process are available in the file. In all correspondences and promotional activities indicating that Altuzan is not suitable for intraocular treatments, this statement in SPC/PIL is a fundamental starting point. In addition, in the opinion dated 26.01.2019 submitted by TOA to AIFD, this statement in Altuzan's prospectus was highlighted by underlining, and the potential risks of intraocular use were emphasized beyond being an off-label drug. Also, in the response of (.....), it was stated that the medical sales representatives implied to the physicians that the use of Altuzan could cause medical malpractice, based on the absence of a statement in the prospectus of the product that the drug can be used intraocularly. It is possible to say that the statement in Altuzan's SPC that it is not suitable for intravitreal use constitutes a strong support for the negative promotions pointed out by the aforementioned Hospital.

(252) **The following statements in the plea: In the evaluations made within the scope of the file, it was stated that there was a 22.4% decrease in the relevant expenditures owing to the HIC amendment dated 28.12.2018. However, in this case, the connection with ROCHE was unclear, because the HIC amendment is exclusively within the jurisdiction of SSI. It is clear that mandating the use of Altuzan will reduce expenditures. Therefore, the SSI's inability to save money by not making arrangements earlier has nothing to do with ROCHE's actions.**

(253) An agreement within the scope of Article 4 of Act No. 4054 can only be exempted from the application of Article 4 if all the conditions in Article 5 of the same Act are met. As mentioned above, it is the patient who uses the drug, it is the physician who prescribes the drug, and it is the state which mostly pays for the drug in the pharmaceutical industry. In this sense, the physicians who are economically insensible to the prices were deterred from using Altuzan, which is more affordable, by the initiatives realized by the common will of the parties. Thus, the health system had to endure a significant cost increase. As a result of the actions of the said

undertakings, in the market of intraocularly applied anti-VEGF molecules, there is no development or improvement within the scope of the subparagraph (a) of Article 5 of the Act No. 4054, on the contrary, within the scope of subparagraph (b) of the same article, irreparable damages emerged in terms of demand, in general terms, before the "consumers". With the HIC amendment dated 28.12.2018, the use of Altuzan in the first-line therapy became mandatory, which resulted in the decrease of 22.4% in the reimbursement amounts of the SSI in the related treatments. This important in terms of proving the harm caused to the consumers by the concerted actions of the undertakings.

(254) **The following statements in the plea: In the lawsuit filed by TOA against the HIC amendment and demanding the stay of execution, after 10th Chamber of the Council of State rejected stay of execution, Plenary Session of Administrative Law Chambers (PSALC) partially approved the request to annul the stay of execution depending on the following grounds: the defendant administrations must be asked whether Bevacizumab would provide a significant advantage over the licensed drugs for intraocular use, and the reasons why the reimbursement of licensed drugs is subject to compulsory first-degree treatment with off-label drugs. Based on the result, a re-decision should be made. Although in the PSALC's decision the administration argued that there is no clinically significant difference in efficacy and safety among the drugs licensed and Bevacizumab, the Guidelines for Off-Label Use of Drugs mentions significant advantage in line with scientific data rather than a significant difference. In this case, ROCHE was accused of being a member of the cartel because it participated in the meetings where AIFD and TOA discussed the issues questioned by PSALC. In the evaluation section of the report, the participation of other undertakings in the meetings was not mentioned. If participation in meetings is sufficient to act jointly, it is necessary to question whether other participants are also involved in concerted action with ROCHE and NOVARTIS. AIFD meetings are not specific to Altuzan/Lucentis. For the first time in Turkey, the use of a product that does not have an approved indication in first line treatment is made mandatory, although there is a drug with an indication, which concerns the entire industry. ROCHE was not even conscious of the meeting on 09.11.2018 to which BAYER, NOVARTIS and AIFD officials attended prior to the HIC amendment. While AIFD, BAYER and NOVARTIS came together in the first of the AIFD meetings, and it was stated in the responses of BAYER and ALLERGAN (Documents 65, 67) that these undertakings held meetings with SSI, physicians and industry associations, ROCHE, who did not take part in any of these, was accused.**

(255) Due to the following reasons, the decision made by the Council of State PSALC was not found compliant with the law: In the reevaluation process of the refusal to stay of execution by the 10th Chamber of the Council of State, the decision was not made by asking the defendant administrations whether the active substance of *Bevacizumab* provides a significant advantage compared to the licensed drugs for intraocular use in line with scientific data and the scientific and medical reasons which require the reimbursement of drug licensed for intraocular use to be subject to mandatory first-line treatment with off-label drugs. This decision does not mean that the relevant provision was annulled, and the litigation on the subject continues.

(256) Even though it is true that ROCHE is not conscious of a meeting of which it is a member and has a representative on the board of directors, this does not affect

the evaluation made regarding AIFD meetings within the scope of the file. Nowhere in the report is it claimed that only ROCHE and NOVARTIS participated in the said meetings and other undertakings did not. Moreover, attending the meetings at AIFD is not considered a violation by itself in the Investigation Report. In this framework, it was found that the parties to the investigation were not only represented by AIFD during the appeal/litigation process, but also came together at events held within or through AIFD. However, this finding alone was not put forward as evidence for the existence of a violation. What is considered a violation is that NOVARTIS and ROCHE is deterred the use of Altuzan by directing the administrative or judicial processes with misleading information by highlighting the risk of endophthalmitis and side effects of Altuzan, in a way that will shift the demand to Lucentis in intraocular treatments by acting jointly and created a perception of difference that does not reflect the truth that Altuzan and Lucentis are different, and in this context, made negative promotions about Altuzan to physicians.

(257) The position taken by AIFD against the HIC amendment, the relationship of the parties to the investigation with AIFD and their participation in the relevant correspondence and meetings together in this process, and how these were addressed in terms of violation evaluation are explained above. On the other hand, it is clear that the HIC amendment dated 28.12.2018 is directly concerns *Eylea's* license holder BAYER, and the steps of this undertaking in objecting to public institutions and taking legal action can be explained by commercial motives. However, the observations made in the licensing and promotion legs of the violation, which is evaluated within the scope of the investigation, are aimed at ROCHE and NOVARTIS. More importantly, the license agreement for *Lucentis* between GENENTECH, a subsidiary of the Roche Group, and NOVARTIS enables ROCHE to indirectly earn income from each box of *Lucentis* sold, in addition to the fixed income, in Turkey and other countries. Therefore, this situation creates a unity of interest between the parties and eliminates the incentive to evaluate the sales potential of *Altuzan*, which could steal from ROCHE's Lucentis sales in ocular treatments. Since this relationship is much more clearly in favor of NOVARTIS, there is no need for an analysis of the anticompetitive gain that this relationship creates for the aforementioned undertaking. In this context, it is unnecessary to question why ROCHE and NOVARTIS are held responsible for the events organized by AIFD.

(258) The e-mails of AIFD Market Access and Health Policy Directors, dated respectively 03.01.2019, 28.01.2019 and 28.02.2019, regarding the HIC amendment, were sent to ALLERGAN, BAYER and NOVARTIS as well as to ROCHE. As stated above, there is no evidence that ROCHE, who appears passive according to NOVARTIS, made a statement or stance to stay out of events and conversations carried out by AIFD related to the subject of investigation. Therefore, ROCHE contributed to the will formed in meetings and relevant correspondences within AIFD both as a director and as a member. In this case, contrary to what is claimed in the plea, it is not possible to argue that ROCHE followed a different stance from AIFD and NOVARTIS on the objection to the HIC amendment.

(259) **The following statements in the plea: The fact that NOVARTIS filed a lawsuit against the HIC amendment was presented as an element of the cartel between the parties. It was not taken into consideration that ROCHE did not act accordingly, and that TOA, Bayer and real persons filed lawsuits as well as NOVARTIS. The constitutional right of action has been acknowledged as an act of restricting competition.**

(260) NOVARTIS filing a lawsuit against the HIC amendment was not considered as an issue against competition in the evaluations made within the scope of the file. In other words, it is not the parties exercising their legal rights that is considered a violation within the scope of Article 4 of Act No. 4054, but that ROCHE and NOVARTIS acted jointly and encourage the use of *Lucentis* among rival products in intraocular treatments and discourage the preference of *Altuzan*, directed/tried to direct the administration/judiciary processes with misleading information and negatively promoting Altuzan to physicians to this end.

(261) **The following statements in the plea: To this day, ROCHE has not lodged a single objection against Altuzan's presence in OLDL. While this is the case, it is not correct to state that ROCHE discouraged the use of Altuzan. Moreover, it was announced in TMMDA's letter dated 17.05.2013, that the use of off-label drugs is not recommended when licensed treatment is possible. Therefore, it was TMMDA itself who discouraged the use of Altuzan. This letter was never mentioned in the investigation report prepared within the scope of the file. Therefore, there cannot be a violation claim lasting until the February 2019 Guideline amendment when this letter became functionless.**

(262) In the evaluations made within the scope of the file, it has already been stated that ROCHE did not file an appeal to the relevant public institutions against the HIC amendment and did not go to court. Therefore, it is clear that ROCHE remains in a more passive position compared to NOVARTIS in terms of formal objections. However, ROCHE is a member and represented by a member in the board of directors in AIFD, therefore AIFD represents ROCHE's will and is expected to protect its interest. Thus, AIFD has filed an objection/litigation against the HIC amendment. Therefore, it is concluded that the will of both parties to the investigation is reflected in the applications made before the administrative and judicial processes. While it was NOVARTIS who is the party to the investigation that directly appealed to SSI and TMMDA and filed a lawsuit against the HIC amendment, the will of ROCHE was also represented in AIFD's initiatives. Still, the parties to the investigation attended/ involved together in many meetings and correspondences before the AIFD. Considering these findings, it is clearly seen that ROCHE and NOVARTIS act parallelly.

(263) In 2011, ROCHE applied to include the phrase *"Altuzan is not suitable for intravitreal use."* to *Altuzan's* SPC and PIL. After *Altuzan's* SPC and PIL were changed as such, TMMDA requested the removal of the relevant phrase in 2018 and ROCHE resisted this request for a long time. TMMDA's request was fulfilled in 2019, after TMMDA stated that the licenses of 100 mg and 400 mg forms of *Altuzan* could be suspended unless ROCHE complied. In this case, it cannot be stated that TMMDA itself discouraged the use of *Altuzan*.

(264) **The following statements in the plea: It is quite natural for Roche Group to have a license agreement with Novartis Group and receive royalties within the framework of this license agreement. There are thousands of examples of this in the industry. ROCHE's refusal to enter the ophthalmic field is due to commercial preferences, not this licensing relationship.**

(265) It is known that there are many examples of license agreements between GENENTECH and NOVARTIS in the Roche Group in the market for medicine for human use. It is also known that license agreements alone cannot be considered restrictive of competition in the absence of some other factors. As a matter of fact, no

such evaluation was made in the investigation report. However, ROCHE and NOVATIS are independent undertakings as they themselves emphasize. Any kind of relationship that may create a joint interest between independent undertakings may constitute an issue of competition law under certain conditions.

(266) There is a licensing relationship between the parties to the investigation. Namely, GENENTECH has transferred the marketing and sales rights of *Avastin (Altuzan)* containing *Bevacizumab* to ROCHE, and the same rights of *Lucentis* containing *Ranibizumab* to NOVARTIS, excluding the USA. According to the license agreement signed between GENENTECH and NOVARTIS, (.....) pays to GENENTECH and therefore, indirectly to ROCHE. ROCHE generates substantial revenue from the sale of its product's rival, *Lucentis*, which is much higher priced. It is clear that this will reduce/perhaps destroy the incentive for ROCHE to actively evaluate the sales potential of *Altuzan*, which is widely preferred in the same treatment areas. Moreover, with the widespread use of *Lucentis*, which is a much higher priced product, instead of Altuzan, it is obvious that the total sales amounts in the relevant market will increase.

(267) In this context, it is not possible to address the legal and commercial relations between the parties to the investigation independent of the subject of the investigation.

(268) **The following statements in the plea: In the evaluation made within the scope of the file, the document, which is stated to show the contact between the parties and referred to in many sections, is an internal correspondence of the Roche Group and does not belong to NOVARTIS. This document dated 2019 regarding the American market was written by GENENTECH, a Roche Group company, which sells Lucentis in the USA. This document came to Turkey and (.....) incorrectly due to the similarity in name.**

(269) As mentioned above, the Excel file named "Lucentis Value Proposition Campaign Plan" in ROCHE covers the marketing policy of Lucentis, sold by NOVARTIS in Turkey, what kind of brand perception it will create, the scope of the value proposition campaign that will be launched in April 2019, what the success metrics of the campaign are, who is in charge of the campaign, their contact information, through which channels the target groups will be reached, what actions will be taken in which periods of 2019, the aims of the brand and the messages it will give to consumers and physicians.

(270) The information apart from the persons involved in the marketing activities and the contact information of these persons is of interest not only to the USA but also to Turkey, contrary to the claim in the plea. These two undertakings should be sensitive about trade secrets taking into account the following reasons: two products found to be in the same relevant product market and in competition are sold by different undertakings that do not belong to the same economic unity. Therefore, even if these two undertakings have various connections abroad, they are rivals within the scope of their structuring in Turkey or in commercial transactions concerning Turkey.

(271) During the on-site inspection, the relevant document was found in the computer of the authorized officer of Roche Müstahzarları San. A.Ş. which makes the sale of Altuzan in Turkey and is registered to Turkish Trade Registry. In this sense, the fact that ROCHE who sells the competitor product have the trade secret document, which contains the marketing strategies for Lucentis product, the sales of

which is made by/ the license of which belongs to Novartis Sağlık Gıda ve Tarım Ür. San. ve Tic. A.Ş., registered to Turkish Trade Registry cannot be explained by the foreign connections of the undertakings.

(272) **The relevance of the documents quoted and explained in paragraphs 54, 55, 60 and 61 of the decision to the subject of the investigation could not be understood.**

(273) The document referred to paragraphs 54 and 55 of the decision and obtained during the on-site inspection relates to an article examined by the ROCHE authorities. In the article in question, by using retrospective trend analysis, the savings made by using Bevacizumab instead of Ranibizumab and Aflibercept from 2008 to 2015 in the treatment of AMD in the USA was estimated to be 17.3 billion USD. In fact, it was stated that provided that the savings achieved with the use of Bevacizumab not only in AMD treatments but also in DME and retinal vein occlusion treatments were examined and estimated within the scope of the study, the total amount of savings would exceed 17.3 billion USD. This article is important in that it shows that ROCHE officials know that the public saves money because of the use of Bevacizumab in the field of ophthalmology and that they know that the public suffers a loss unless it is used. In addition, it is clear that ROCHE, who argues that it has no commercial interest in the ophthalmology field, is not indifferent to the treatment of ocular diseases, and that the issues relevant to the investigation are within its area of interest. Moreover, it is noteworthy that the person who sent the e-mail in question to ROCHE officials was Roche Health Economics & Market Access Manager, not any company employee.

(274) The document mentioned in paragraphs 60 and 61 of the Decision, however, is important in order to understand the market presence of the examined products of the undertakings under investigation. In the Excel file attached to the e-mail in question; according to sales data, *Altuzan* was among the top ten products of ROCHE in Turkey in 2018 and even ranked (.....) in hospital channel, whereas *Lucentis* ranked (.....) in the pharmacy channel, and when hospital and pharmacy channels are considered together, *Altuzan* ranked (.....).

(275) **The following statements in the plea: ROCHE found out about the Van case for the first time from the report. However, it was stated in the report that the Van case was known and Kırıkkale case was highlighted. After the Kırıkkale case regarding endophthalmitis and vision loss in many patients after the HIC amendment, the sale of the relevant series of Altuzan product stopped throughout the country on suspicion of manufacturing defect. Despite being provided with written information, the Committee did not include a single statement on this issue in the report.**

(276) Based on the Van case, in the Investigation Report, the safety of Ranimizumab was not open to discussion, and it showed that the intraocular administration of anti-VEGF agents always involves certain levels of risk, and that this is not only valid for *Altuzan*, but also the use of *Ranibizumab* may have negative outcomes. As a result, although it is concluded in the Investigation Report that various risks may arise in the use of both *Altuzan* and *Lucentis*, there is not a conclusion that any risk will not arise in the use of *Altuzan*. Only the similarities of the *Altuzan* cases in Kırıkkale and *Lucentis* cases in Van are mentioned.

(277) **The following statements in the plea: In the report, it is stated that Altuzan can be used by apportioning it for 60 patients, referring to the articles**

of TMMDA and SSI. However, in the letter dated 30.07.2018 sent to the SSI by TMMDA, it was stated that a vial can be divided into 5-10 doses, which was not included in the report.

(278) Considering the amount applied and wastage for each patient, it is understood that 100 mg form of Altuzan can meet the needs of 60 patients at most. However, this number is lower due to the fact that for safety reasons, the drug must be consumed on the day it is opened and generally a smaller number of patients is administered. SSI has bent this practice so that a vial can only be used for a single patient when necessary. Even when this is the case, there is a significant cost advantage for the state and the patient when compared to the Lucentis administration. In this context, the objection of the party is not meaningful.

(279) **The following statements in the plea: Responses of third parties whose opinions were sought during the investigation phase are included in a way that restricts the right of defense. For example, although almost all of the hospitals responded that no event deterring the use of Altuzan was organized by ROCHE, this was not mentioned in the evaluation. In the evaluations made within the scope of the file, it is known that ROCHE sent a letter dated 23.01.2019 through AIFD and requested TOA's opinion. However, AIFD declared that it made a request for TOA's opinion with its own Board of Directors decision.**

(280) Contrary to the claims of the party, the responses of third parties were conveyed as broadly as possible in the investigation report. Written statements of AIFD and TOA, which made similar statements with the parties to the investigation on certain issues, were also utilized within this framework. In line with this understanding, a separate section titled "Information and Opinions Submitted by ROCHE on the relevant Product Market "is included under the "Related Market" section above. Therefore, it should not be possible to argue that the contents of the documents in the file are weighted in accordance with the opinions of the Investigation Committee.

(281) By examining the information and documents in the file, it is concluded that NOVARTIS actively took part in promoting the concerted action to the physicians, which is the subject of the investigation. In other words, it is not concluded that ROCHE has made negative promotion regarding the intraocular administration of Altuzan. Therefore, the way the hospital responses are reflected does not limit ROCHE's right of defense in terms of the relevant findings. On the other hand, the quoted responses are included in the appendix of the investigation report, with only the name of the hospital obscured and the content of it in a few documents, except for the restricted parts. Thus, ROCHE can file an objection using the relevant documents. On the other hand, although some reservations about the use of Altuzan were expressed in the responses of hospitals, it was also stated that this product could be used effectively in relevant treatments and seriously be preferred by some hospitals even before the HIC amendment.

(282) For example, it is stated in the evaluations made within the scope of the file that the private hospitals, which were consulted within the scope of the investigation, used Altuzan in significant amounts in the relevant treatments before the HIC amendment. For example, the rates of Altuzan use before the HIC amendment vary between 60% and 90% in private hospitals, which were consulted during the investigation, and also in three public hospitals. Issues such as the following were mentioned by public hospitals: There is no significant difference

between *Altuzan* and other anti-VEGF agents in terms of efficacy and safety. Depending on the stages or types of diseases, the usage patterns and application doses of the drugs in question do not change, while the frequency of application may vary. Although the apportioning *Altuzan* into doses is done in the operating room environment, the withdrawal of the drug from the vial into the syringe increases the risk of contamination for every patient. Physicians are worried that patients will file medical malpractice lawsuits after such practices. Therefore, they have reservations about the use of *Altuzan*. If it is possible to present *Altuzan* in a sterile syringe that can be administered to a single patient, like other drugs, such concerns can be prevented. Pharmaceutical sales representatives have implied that the use of this drug may cause medical malpractice to physicians, based on the fact that there is no indication in the *Altuzan* package insert that the drug can be used intraocularly.

(283) **The following statements in the plea: The right of defense was restricted by rejecting the request for the examination of many documents upon access to the file. The most striking of these is the denial of access to NOVARTIS' statements. In the relevant decision, the Board stated that the document referred to in the report was not in the nature of evidence. In this case, the final Board decision cannot be based on this statement. In addition, the replies sent by the SSI were not made accessible, as they were not found to be exculpatory or accusatory. In order to use the right of defense, it is necessary to explain in which parts of the report the documents that are not accessible are used.**

(284) Although the parties have the right to access the file within the scope of the Communiqué on the Regulation of the Right of Access to the File and the Protection of Trade Secrets (Communiqué No. 2010/3), it is not possible to state that this right is unlimited. As a matter of fact, the parties have the right to access the file except for internal correspondence and trade secrets and other confidential information regarding other undertakings, associations of undertakings and individuals within the scope of the right to access the file. In this context, the requester is provided with the opportunity to access all kinds of documents and information obtained about them within the Authority. The detection of the documents that cannot be accessed was also made by the Board as stated in the Communiqué No. 2010/3 and the parties were notified of the denial. Denial of access to information/documents that constitute an exception to access to the file will not be considered as a violation of the right of defense. In this sense, if the relevant decision is claimed to be not in accordance with the law, application for judicial remedy regarding the decision is possible. There is no document that was not made accessible in accordance with the afore-mentioned Board decision.

(285) **The following statements in the plea: The Committee made its first request for information 10 months after the start of the investigation. Then all relevant information and documents were examined and evaluated by the Committee within seven days. Due to this congestion, the incorrect assessments of TMMDA (Document 91) were accepted as they are.**

(286) The objection regarding the TMMDA’s letter is answered above. On the other hand, while it is claimed that the Investigation Committee made an incomplete examination in a limited time, attention was drawn to the dates of access on the internet to the scientific studies used in the report. These dates are 05.06.2020 and 08.05.2020.

(287) Contrary to what is believed, the dates specified as "Accessed" do not indicate the dates when the relevant internet addresses were accessed for the first time or when the resources at the relevant addresses were read. These dates show the last time the internet addresses provided in the footnotes were checked whether they are still valid. The links of the resources accessed on the internet may change, and an internet address that was previously accessible may become inaccessible later on. In such cases, the addresses accessed must be updated.

(288) In order to show the undertakings party to the investigation the last access date for the internet addresses mentioned, whether they were still accessible was checked close to the date when the parties would be notified of the Investigation Report. In addition, the dates the afore-mentioned addresses were last accessed were specified as “Accessed”.

(289) During the investigation period, information was requested not only from ROCHE, but also from various public institutions and many undertakings operating in the pharmaceutical industry. In this context, the information, and documents to be used for the investigation were obtained and evaluated during the investigation period.

I.4.3.2. The Plea of NOVARTIS and its Evaluation

Arguments against the Allegations in the Investigation Notification

(290) **Following statements were made: The ICA decision referred to in the Investigation Notification concerns the Italian market and the activities in this market, and the link between the two cases in the current file and how the Italian case would impact Turkey are not specified. The approaches of the administrative authorities and the conditions in the Turkish and Italian markets are different. Therefore, for NOVARTIS, the decision regarding Italy is in no way connected with the investigation in Turkey.**

(291) Within the scope of the investigation, the decision of ICA was taken into account in the conclusion that the undertakings under investigation were carrying out the same global strategy in some countries, including Turkey. The existence of the violation was not determined on the basis of this decision alone. The afore-mentioned decision is also briefly included in the relevant product market section, together with the decisions taken by the authorities of other countries (United Kingdom, France, Spain), since it is an authority decision on a subject similar to the investigation conducted in Turkey. However, the detection of the relevant product market was not based solely on the decision of the ICA authority. The evaluations made within the scope of the file were made about the following issues: ROCHE and NOVARTIS acted jointly and encouraged the use of Lucentis which is among rival products in intraocular treatments and discouraged the preference of Altuzan, directed/tried to direct the administrative/judicial processes with misleading information and made negative promotions about Altuzan to the physicians to this end. It is concluded that the parties in Turkey also acted in accordance with the case examined in Italy. Detailed information on the subject is given in the evaluation section.

(292) **Following statements were made: A complaint was filed with the Brazilian Competition Authority (BCA) in 2015, based on the Italian decision, and after the preliminary inquiry the BCA conducted in 2017, the investigation discontinued because there was no evidence of restrictive of competition activities and no grounds to continue the investigation**.

(293) The decision of the ICA is not the only basis for the evaluation regarding the existence of the violation in the investigation conducted in Turkey. Detailed explanations on the subject and relevant documents are included in the evaluation section.

(294) **Following statements were made: The shareholding relationship between the parties, which does not give the right to control, cannot be considered as an agreement restricting competition**.

(295) GENENTECH has transferred the marketing and sales rights of Avastin (Altuzan) containing Bevacizumab to ROCHE, and the same rights of Lucentis containing Ranibizumab to NOVARTIS, outside the USA. According to the license agreement signed between GENENTECH and NOVARTIS, NOVARTIS pays to (.....) GENENTECH and indirectly to ROCHE. It is possible to say that the legal and commercial relations between the parties to the investigation constitute the economic foundations of the global strategy, which is also reflected in the Turkish market for medicines for human use. In fact, ROCHE generates a significant revenue from the sales of Lucentis, a competitor of its own product and moreover, much higher priced product. It is clear that this will reduce/perhaps destroy the incentive for ROCHE to actively evaluate the sales potential of Altuzan, which is widely preferred in the same treatment areas. Furthermore, it is clear that the widespread use of Lucentis, which is a much higher priced product instead of Altuzan, will increase total sales in the relevant market.

(296) **Following statements were made: The claim that there is communication between the employees of the companies in the Italian subsidiaries of the parties with the aim of creating "artificial product differentiation" between Lucentis and Avastin products is not true. The products are different from each other. The assumption that "two products are the same", which is the basis of the ICA decision, contradicts science. The Italian Medicines Agency (AIFA) also confirmed that it was a wrong decision.**

(297) While identifying the relevant product market within the scope of the file, scientific studies and authority decisions regarding whether active substances are in a substitution relationship with each other in terms of treatment of ocular diseases were examined and the information obtained from ophthalmologists was evaluated in order to determine the demand-side substitution relationship. In this context, it is concluded that Avastin and Lucentis can be used as substitutes for each other. There are many scientific studies showing that Bevacizumab does not differ statistically on a significant level from Ranibizumab and Aflibercept in terms of efficiency and that they are also similar in terms of side effects. Detailed explanation regarding this subject is mentioned in “Relevant Product Market” section.

(298) **Following statements were made: NOVARTIS's attempt to prevent the off-label use of Avastin in AMD treatment is a legal and legitimate status vis a vis including a cancer drug in reimbursement for its use in unlicensed ocular indications and making it mandatory in the first-line therapy.**

(299) The strategy of NOVARTIS on the subject is also evident in its objections to SSI and TMMDA, and the lawsuits it filed against the amendment on Healthcare Implementation Communique dated 28.12.2018. Again, one of the main pillars of NOVARTIS’ arguments was this misleading information that Altuzan is not suitable for intravitreal use, which differed from the original expression. However, that a drug is not suitable for intraocular administration and that it is not formulated for intraocular

administration do not mean the same thing. The different translation is considered to be a part of a strategy to disseminate misinformation about Avastin. As a matter of fact, this statement in the SPC/PIL and the other statements supportive of this were used as a basis for both negative promotions to physicians and objections/litigations before administrative and judicial authorities.

(300) On the other hand, according to the written statement of the SSI, the argument that the use of this drug in intraocular treatments leads to endophthalmitis comes to the fore due to the negative promotion of Altuzan. However, in the response SSI sent, it was stated that there was no detection of adverse effects as among 15,000 patients who received Bevacizumab, as claimed.

(301) In this context, what is qualified as a violation within the scope of the Article 4 of the Act No. 4054 is not the fact that the parties are exercising their legal rights, but the fact that ROCHE and NOVARTIS act jointly and encourage the use of Lucentis among competitor products in intraocular treatments and discourage the preference to Altuzan, directed/tried to direct the administration/judiciary processes with misleading information and made negative promotions about Altuzan to physicians to this end.

Explanations Regarding the Companies under Investigation and the Shareholding Structure and Commercial Relations of these Companies

The statements are as follows:

- **Novartis AG never had a representative on the board of directors or decision-making bodies, with the exception of the general assembly of Roche AG shareholders. Novartis AG does not have any rights of management or right to obtain information beyond the rights all shareholders have. Novartis AG has no right or authority to affect the management, operations, and agreements of Roche AG directly or indirectly.**

- **In joint stock companies established in Switzerland, the board of directors takes decisions on all matters that are not left to the authority of the general assembly. The general assembly does not have the authority to give any instructions to the board of directors regarding the management of the company. Novartis AG never had a representative on the board of directors of Roche AG and had no role in the management of or supervising Roche AG's business.**

- **Novartis AG has less than 33.33% of voting rights in Roche AG, which is not enough to appoint any board member of Roche AG. Novartis AG has no specific veto right or other specific rights. Novartis AG has the voting rights of any minority shareholder.**

- **It is stated that Novartis AG has no control over Roche AG in the decisions of the Commission[81] and the Bundeskartellamt[82].**

(302) Within the scope of the file, there was not a determination on the fact that Novartis AG has control over Roche AG.

Explanations Regarding Commercial Relations

The statements are as follows:

[81] Decision no. COMP/M.4049, Novartis/Chiron, para. 46.
[82] Decision no. B3 11/03, para. 17.

- **License and Cooperation Agreement (LCA) was signed between Novartis Ophthalmic AG (is stated to merge with Novartis Pharma AG) and Genentech Inc. in 2003. The purpose of the LCA is the development and commercialization of *Ranibizumab*, which is currently *Lucentis*.**

- **Under the LCA, Genentech Inc. granted NOVARTIS royalty to develop and commercialize *Ranibizumab* outside of the USA. Responsibility of the development and commercialization of *Ranibizumab* in the USA remained within Genentech Inc. In the pharmaceutical industry, similar agreements are often seen in regions or treatment areas where the grantor of a license does not have sufficient experience or activity.**

- **Any competition authority that reviewed the LCA did not detect any issues regarding the LCA. The commercial relationship between the parties did not result in any cooperation or communication beyond what is mandatory and legitimate under the provisions of the LCA.**

- **NOVARTIS' income from the sale of *Lucentis* is completely separate and independent from the dividend income it receives from its share in ROCHE.**

(303) GENENTECH has transferred the marketing and sale rights of *Avastin (Altuzan)* which contains *Bevacizumab* to ROCHE, the same rights of *Lucentis* which contains *Ranibizumab* to NOVARTIS outside of the USA. According to the license agreement signed between GENENTECH and NOVARTIS, NOVARTIS (.....) pays GENENTECH and indirectly to ROCHE. It is possible to say that the legal and commercial relations between the parties to the investigation form the financial basis of the global strategy mentioned above, which is also reflected in the Turkish market for medicine for human us because ROCHE earns a significant income from the sales of *Lucentis*, a rival of its own product and furthermore, which is much higher priced. It is clear that this situation will diminish/ maybe even destroy ROCHE's incentive to actively evaluate the sales potential of *Altuzan* which is widely preferred in the same treatment fields. Furthermore, it is obvious that the widespread use of *Lucentis,* which is a much higher priced product, instead of *Altuzan* will increase total sales and the drug expenditures in the relevant market.

Explanations Regarding the Drugs under Investigation

The statements are as follows:

- ***Avastin* and *Lucentis* have similar mechanisms of action. However, they were developed for the treatment of completely different diseases and were tested separately in clinical studies for these different diseases.**

- ***Avastin* was developed to suppress VEGF expression for the prevention of tumor growth and metastasis in patients with cancer. It is used in combination with other cancer drugs. *Lucentis*, on the other hand, was developed for use as a stand-alone treatment or in combination with treatments like laser photocoagulation in patients with visual impairment due to neovascular AMD and DME, macular edema due to retinal vein occlusion (RVT), and choroidal neovascularization (CNV) due to pathological myopia to prevent the formation of new blood vessels in the eye.**

- **Lucentis and Avastin are completely different molecules. They have different profiles in terms of production, biochemical properties, pharmacology, manufacturing and formulation, packaging, indications,**

licensing status and clinical evidence.

- **Due to its molecular weight, Avastin is not rapidly cleared from the kidneys, stays in the bloodstream longer and suppresses the VEGF more in the patient. Such suppression of VEGF can result in slower or poor wound healing, difficulty in forming new blood vessels, hypertension, arterial thromboembolic events, cardiomyopathy, hemorrhage, gastrointestinal perforation, and other potential side effects.**

- ***Ranibizumab* has one-third the molecular weight of *Avastin*, results in a much lower ocular half-life, high retinal layer penetration and higher binding affinity to VEGF protein. These properties indicate that *Lucentis* is rapidly cleared from the systemic circulation and has little effect on the free circulation of VEGF in blood plasma. Systemic exposure is approximately 70 times lower than for *Lucentis* after quarterly injections. Therefore, when Lucentis is applied ocularly, it enables targeted activity.**

- ***Avastin* was never developed for ophthalmic use. The relevant risk-benefit analysis for the respective indication was taken into account. Therefore, *Avastin* was never subjected to the rigorous clinical trials required for the approval for ophthalmic use. Consequently, there is no overlap in licensed indications between *Lucentis* and *Avastin*.**

- ***Avastin* needs to be divided into smaller dosages so that vials designed for oncological use can be administered as intravitreal injection for off-label ophthalmological use. Preparing drugs by separating them into vials for intravitreal use causes disruption of sterility and an increased risk of bacterial contamination, and also drug preparation in the pharmacy brings the potential for errors due to incorrect or inadequate procedural practices.**

- ***Lucentis,* however, was developed for ophthalmic use. Due to the limited space in the eye, *Lucentis* was reconstituted anew so that it could bind to its target VEGF more tightly. It is now produced in disposable protective vials and pre-filled syringes to prevent contamination and ocular infections. It also meets strict manufacturing standards for ophthalmic solutions.**

- **These important molecular and pharmacological differences between *Avastin* and *Lucentis* lead to different developments and license approval processes for different therapeutic indications and uses. These differences in indications have turned into a completely different formulation and there are also differences in the dosages of the products and the way of administration. The production of both products is subject to different legal regulations. This means that, the licensed (designed for oncological use) form of *Avastin* described in the SPC should necessarily be modified fundamentally in off-label ophthalmic use.**

(304) While there are differences between *Avastin* and *Lucentis* (such as molecule, molecular weight), such differences are not considered to be an obstacle for the afore-mentioned drugs to exist in the same product market. While determining the relevant product market, scientific studies and authority decisions regarding whether the active substances are equivalent of each other in terms of treatments for ocular diseases were reviewed and information obtained from ophthalmologists was evaluated in order to determine demand-side substitution relationship. As a result, it is concluded that *Avastin* and *Lucentis* can be used as substitutes for each other.

There are numerous scientific studies showing that *Bevacizumab* does not differ statistically on a significant level from *Ranibizumab* and *Aflibercept* in terms of efficiency and that they are also similar in terms of side effects. Detailed explanation regarding this subject is mentioned in “Relevant Product Market” section.

Explanations Regarding the Off-label Drug Use concerning Avastin

The statements are as follows:

- **The off-label use of Avastin for ocular disease indications is controversial and has been the subject of intense debate in other countries.**

- **Off-label drug use is often preferred because of patients' unmet medical needs, especially in the absence of a licensed treatment option. However, recently, public institutions have a clear tendency towards off-label use of some drugs and this use seems to be based on financial reasons. This led to questioning the purpose and integrity of the licensing system as well as the possible balance between patients' health and financial gains.**

- **The legislation in Turkey prohibited the marketing of unlicensed drugs. The exception to this rule, which is subject to strict conditions and is very limited, is the use of off-label drugs if the conditions determined by the Ministry of Health are met.**

- **However, although the risks posed by off-label drug use were acknowledged, the explicit rule "*Should there is a treatment option for approved products in Turkey, off-label use is not permitted*" was removed from the OLDL Guidelines updated on 08.02.2019. A change was made in a different direction from the previous applications and tendencies that is “*For diseases that can be treated with drugs included in the approved indication in our country, off-label drug use is assessed by the Authority only if there are treatment options that provide a significant advantage in line with scientific data. Also, the use of the drugs included in the ‘List of Off-Label Drugs That Can Be Used Without Additional Approval from TMMDA’ in the indications included in this list is found convenient by the Authority, and there is no need to apply to the Authority for the request to use off-label drugs on a patient basis.”***

- **“Significant advantage" is not defined in the afore-mentioned Guidelines. Yet, it must be medical advantage by nature and must be more than "increased benefit". However, there is no obvious advantage that requires the off-label use of *Altuzan* over the licensed *Lucentis*. Although there is a licensed alternative to the active substance *Bevacizumab* for ocular diseases, the Ministry of Health included it in the List of Off-Label Drugs That Can Be Used Without Additional Approval from TMMDA for a long time.**

- **The approach of the administrative authorities in Turkey regarding the use of off-label drugs changes from time to time, and they make decisions that contradict their own rules specific to *Bevacizumab*.**

- **The sole intention of NOVARTIS is to ensure that *Lucentis*, which is licensed for ocular diseases and therefore was approved for its efficacy and safety, is used legitimately in the market for the indications for which it is licensed; unlike *Altuzan*, which is used off-label by dividing a vial for many patients for financial purposes only, with a method that poses risk for both the**

safety of the patients and compliance with the legislation, and became mandatory in the first-line treatments for reimbursement in ocular indications after December 2018.

- **If NOVARTIS had avoided taking any legal actions at the beginning of 2019 against the SSI decision that included *Altuzan* in reimbursement as mandatory first-line treatment in relevant ocular diseases despite the differences between the two drugs, NOVARTIS' ethical and legal stance would have been questioned.**

- **It is necessary to evaluate the activities of companies that are independent of each other, separately for each country by taking into account the material facts in the country in question.**

- **Considering the evolution of the regulations of the health authorities in Turkey over time, the actions of NOVARTIS are legal and legitimate, and in line with the natural flow of life.**

(305) The strategy of NOVARTIS on the subject is also evident in its objections to SSI and TMMDA, and the lawsuits it filed against the amendment on Healthcare Implementation Communiqué dated 28.12.2018. Again, one of the main pillars of NOVARTIS' arguments was this misleading information which differed from the statement in the original expression that *Altuzan* is not suitable for intravitreal use. It is clear in the investigation report that the will of both parties to the investigation is reflected in the applications made before the administration and judiciary. According to the information obtained from AIFD, meetings were held, and correspondences were made within the body/organization of the association before the objections to the HIC amendment and ROCHE and NOVARTIS attended these events. The briefings of AIFD about the process were delivered to the directors of ROCHE and NOVARTIS as well. Within this framework, the parties to the investigation were not only represented by AIFD, but also came together in events held within or through AIFD during the objection/litigation process.

(306) NOVARTIS was the party to the investigation which directly objected to SSI and TMMDA and filed a lawsuit against HIC amendment, the will of ROCHE was also represented in AIFD's initiatives. Furthermore, the parties to the investigation attended/involved together in many meetings and correspondence before AIFD. As a result of these findings, it is not possible to say that ROCHE and NOVARTIS party to the investigation independently. The fact that ROCHE and NOVARTIS acted jointly and encouraged the use of *Lucentis* among rival products in intraocular treatments and discouraged the preference to *Altuzan*, directed/tried to direct the administration/judiciary processes with misleading information and negatively promoted *Altuzan* to physicians is described as violation within the scope of Article 4 of the Act No. 4054.

Other Explanations

- **There is no evidence to date that the parties are in agreements restrictive of competition. There is no cooperation other than those necessary for the proper conduct of the legitimate LCA.**

- **Considering the fact that *Altuzan* is used off-label by dividing from a vial and injecting into the eye for ocular indications without being subject to any regulatory rule/protocol and there is not a pharmacy for special practices (compounding pharmacy) system, which can reduce the risk to patients' health**

even a little bit due to the dividing the vials, there are real and serious concerns and hesitations that the use of *Altuzan* in ocular indications may cause safety problems, as brought up by scientific discussions. For this reason, off-label use of *Altuzan* continues to be a problem and the competent health authorities should give priority to the health care needs of patients, and this issue is not a matter of competition law.

(307) It was concluded in the case subject to the investigation that ROCHE was active in licensing while NOVARTIS was active in the promoting to the physicians. While it was NOVARTIS who directly objected to SSI and TMMDA and the party to the investigation filing a lawsuit against the HIC amendment, ROCHE's will was also represented in AIFD's initiatives. Furthermore, the parties to the investigation attended to/involved in a number of meetings and correspondences jointly before AIFD. As a result of these findings, it is not possible to say that ROCHE and NOVARTIS acted independently of each other during the case under investigation. Also, document containing trade secrets about *Lucentis*' marketing strategy was found during the on-site inspection at ROCHE. The fact that such a document related to one of the products under investigation is found in the supplier of the rival product clearly shows that parties are in communication about the investigation. It is also found that ROCHE and NOVARTIS come together for the subject of the investigation in the events held under the body of/through AIFD. It is not possible to provide a reasonable explanation for this situation from the perspective of competition law. In this context, the argument that the parties do not have any cooperation other than what is necessary for the proper execution of the LCA is invalid.

(308) While the chronology of the events, academic studies and doctor practices as well as the court decisions, public regulations and court decisions encourage the use of Bevacizumab in intraocular treatments, ROCHE's failure to actively assess its sales potential in this area is incomprehensible in terms of the strategic choices and commercial interests of an undertaking that is expected to act independently. Since Bevacizumab which has a serious price advantage when compared to Ranibizumab, it should be expected that steps be taken to evaluate the aforementioned income potential in commercial terms whereas ROCHE acts in the opposite direction, arguing that its product is not suitable for use in related treatments, does not request the addition of these indications to the license, and does not develop single-use forms for these treatments. NOVARTIS, on the other hand, practices negative promotion about rival product Avantis/Altuzan before physicians and public authorities and raises objections in administrative and judicial processes.

(309) As a result, the fact that NOVARTIS and ROCHE discouraged the use of Altuzan by directing the administrative or judicial processes with misleading information by highlighting the endophthalmitis risk and side effects of Altuzan in a way that will shift the demand to Lucentis in intraocular treatments by acting in harmony, their efforts to create a perception that Altuzan and Lucentis are different, which does not reflect the truth, and in this context, making negative promotions about Altuzan to physicians are considered to be violating Article 4 of the Act No 4054.

(310) **The following statements in the plea: Using countries with different health care legislation and market structure as examples in the evaluations made within the scope of the file means ignoring the realities of Turkey. For example, in the USA, the biggest buyer is not the state, but private insurance companies, and there are private pharmacies where various drugs are divided**

under sterile conditions. The use of off-label Bevacizumab instead of licensed product alternatives in Italy, France and England, which are referred to in the report, is not encouraged by the administrative authorities. None of the referenced studies suggest that Altuzan is superior to Lucentis. Incorrect inferences were made regarding these without considering the details. The ICA decision, whose appeal is still ongoing, has no connection with Turkey and does not constitute evidence for our country.

(311) It is not stated that the ICA decision was finalized. There is a reference to the decision only. The fact that the appeal process of a competition authority decision is ongoing does not invalidate that decision, nor does it mean that it cannot be referred to.

(312) The French Competition Authority announced on its official website with the press release on 09.09.2020 that NOVARTIS, ROCHE and Genentech were sentenced a total of 444 million Euros of administrative fine on the grounds that they abused their dominant position jointly to maintain the sales of Lucentis to the detriment of Avastin in the ophthalmology field.83

(313) In addition, in the evaluations made within the scope of the file, nowhere is it suggested that Altuzan is superior to Lucentis in the relevant treatments. In the referenced studies, it is concluded that there are no statistically significant differences between these products in terms of efficacy. This is confirmed by the relevant authorities, TMMDA and SSI. At this point, it is seen that the discussion is not conducted on a scientific basis, as there are no studies proving the contrary of these scientific findings within the scope of the plea made against the evaluations and determinations including the scientific findings.

(314) **The following statements in the plea: Lucentis and Avastin are two different drugs, the opposite opinion was proposed by TMMDA and SSI. According to the ATC-3 classification, indications and active substances to be considered, these products are not available in the same market. While Altuzan, Lucentis and Eylea are in the same relevant product market, Zaltrap with the same active substance as Eylea is not included in this market definition. While the statement of Sanofi that this drug is not used in the field of ocular treatments was found acceptable, the fact that Altuzan, which contains an active substance different from Lucentis, is not accepted as a licensed drug in the treatment of cancer. This is an inconsistent approach. The statement of SSI that no problem occurred in the application of Bevacizumab in 15,000 patients is a rumor. There is no scientific study conducted by SSI or any other institution on this subject in the file.**

(315) Statements with similar content regarding the definition of the market are evaluated above. In this respect, in line with the information and evaluations given above and world practices, there is no uncertainty that Altuzan and Lucentis are in the same relevant product market. On the other hand, it is beneficial to remind some documents of the parties quoted/summarized above and therefore are within the knowledge of NOVARTIS:

- In the NOVARTIS document included in paragraph 31 above, quotations are made from the opinion of TOA conveyed to AIFD. In TOA's opinion, which the

[83] https://www.autoritedelaconcurrence.fr/en/press-release/treatment-amd-autorite-fines-3-laboratories-abusive-practices, Accessed: 15.09.2020.

investigaton parties frequently refer to, it is stated that *Bevacizumab* is an active product in terms of the specified diseases, with the annotation that not as much as licensed products. In another NOVARTIS document mentioned in paragraph 36, it is stated that one of the countries where the use of *Bevacizumab* in intraocular treatments is common is the USA. From the statements that follow the document, it is understood that this product is also cheaper than *Lucentis* in the USA.

- NOVARTIS internal correspondence included in paragraph 37 of the decision shows that approximately 100 (boxes) of *Avastin* are used monthly in Trabzon Karadeniz Faculty of Medicine. The document dated 03.09.2015 is an example of the fact that this drug was preferred in public hospitals in 2015, long before the HIC amendment.

- In the NOVARTIS internal correspondence referred to in paragraph 39 of the decision, it is stated that clinical experience and some studies contain contractual determinations, but in the articles in 2017-2018, especially from developing countries, there are statements that the use of *Bevacizumab* is cheap and the risk of endophthalmitis, if applied in appropriate sterile conditions, is similar to other anti-VEGFs.

- NOVARTIS internal correspondence quoted in paragraph 40 of the decision mentions the use of *Bevacizumab* in Israel and the USA and *Ranibizumab* and *Aflibercept* are referred to as "approved options" of *Bevacizumab*.

- In TOA's response summarized in paragraph 82 of the decision, it is stated that *Avastin* is used in relevant treatments in the USA, Israel, England, and Italy within the measures taken to minimize the risk of infection.

(316) In this respect, the documents found in NOVARTIS show that this undertaking closely follows not only the HIC amendment, but also the use of Altuzan in intraocular treatments in the world and in Turkey. This contradicts the statement that Altuzan and Lucentis are not rivals.

(317) On the other hand, in the readings made within the scope of the file, it was seen that the use of Zaltrap in intraocular treatments was evaluated in a few of the studies comparing anti-VEGF agents. However, studies in this field in the world are too few to compare with those related to Avastin/Altuzan. Therefore, Zaltrap is not included in the relevant product market definition. Besides, it should be noted that even if Zaltrap was accepted in the same market, this would not change the fact that the parties to the investigation were in concerted action.

(318) On the other hand, since SSI is the relevant public authority on the subject, it provided the results of the study it did in its field within the scope of the file, and the results provided by the relevant public authority are used in the file. It is clear that the information and documents provided by a competent public authority to another public authority within the framework of cooperation cannot be qualified as a rumor.

(319) **The following statement in the plea: No data on off-label use of *Altuzan* could be provided.**

(320) Within the scope of the file, information about the off-label use of *Altuzan* was collected from many public hospitals and university hospitals. Important information on this subject was obtained from the competent authorities, which are SSI and TMMDA, and it was included in the decision and the content of the file.

(321) In addition, there are examples from many countries of off-label use of *Avastin* in relevant treatments. In Turkey, it was stated that private hospitals, which were consulted, used *Altuzan* in significant amounts in the relevant treatments before the HIC amendment. For example, in private hospitals, which were consulted during the investigation, the rate of *Altuzan* usage before the HIC amendment varies between (.....)% and (.....)%. Before the HIC amendment, *Altuzan* was among the drugs preferred by the three public hospitals, which were consulted, and the rate of use in one of them was (.....)%, ranking first by far. On the other hand, reimbursement amounts for off-label use of *Bevacizumab* were also evaluated. In this context, it was not possible to agree with the objection of the party.

(322) **The following statements in the plea: The claim that significant decrease in costs was achieved after the HIC amendment is unrealistic. Especially considering the fact that one box of *Altuzan* was used for a single patient, the statement that there was a cost difference of 30-40 times is quite exaggerated.**

(323) Information on reimbursement amounts and costs in intraocular applications was naturally obtained from SSI, the relevant public authority. According to the information provided by the SSI, significant savings (at the rate of 22.4%) were achieved in the expenditures made for the relevant treatments after the HIC amendment. On the other hand, one vial of *Altuzan* can be used for a single patient in relevant treatments. Even so, the cost of treatment is significantly reduced compared to the use of *Lucentis*. In cases where one vial is used for more than one patient, the cost per patient is even more reduced.

(324) Although it is mathematically possible to obtain 80 doses of *Altuzan* from its 100 mg form and 320 doses from its 400 mg form, it is discovered within the scope of the investigation that the 400 mg form is not used in ocular treatments. Since the single intraocular dose for *Bevacizumab* is 1.25 mg, 80 doses can be obtained from the 100 ml form of *Altuzan*. However, the following information was also obtained within the framework of the interviews conducted within the scope of the investigation: There was wastage during use and a maximum of 60 doses was obtained from a vial. There were not so many patients on the same day in practice and this number was much more limited even if the drug was divided.

(325) Even if 100 mg of *Altuzan* is used in a single patient and a large part of the drug that is not required for treatment goes to waste, *Altuzan* provides a significant cost advantage in terms of public expenditures compared to *Lucentis*. Therefore, regardless of the outcome of the discussion on how many patients a box of *Altuzan* can be used, it is obvious that *Altuzan* is a much more suitable alternative in terms of public expenditures.

(326) **The following statements in the plea: Other than the correspondence at the end of 2018 regarding the violation that allegedly started in 2011, no evidence was included in the evaluations made within the scope of the file. Extreme meaning was attributed to the process of *Altuzan's* (Summary of Product Characteristics) SPC amendment and the slight difference in meaning in the SPC. NOVARTIS has no role in this process. Even if the existence of a violation is assumed, it must have started on 28.01.2019, when the HIC amendment, due to which the parties became rivals entered into force.**

(327) The parties did not become rivals in 2019, when the HIC amendment entered into force. As stated above, two of the private hospitals and three of the public

hospitals, which were consulted during the investigation, reported that they used *Altuzan* in the relevant treatments even before the HIC amendment.

(328) In financial terms, competition means that two products can be used as substitutes for each other. Therefore, whether two products are competing or not is determined not by public regulations, but by evaluating especially demand substitution, supply substitution and potential competition. In this respect, concrete attempts of undertakings to shift the demand for one product to another, regardless of whether these attempts are made before the public or not, can be taken as a basis in evaluating the rivalry of two products.

(329) ROCHE made the first application to TMMDA on 29.12.2011 for the SPC/PIL amendment, including the addition of the statement that *Altuzan* is not suitable for intravitreal use. As given below, in the evaluation regarding the duration of the violation, it is accepted that the violation started with this development. Information and documents obtained from ROCHE regarding this process are available in the file. In all correspondence and promotional activities on the fact that *Altuzan* is not suitable for intraocular treatments, this statement in SPC/PIL was a fundamental starting point.

(330) As summarized above, it was stated in the plea that the statement in *Altuzan'*s SPC that the product is not suitable for intravitreal use was given much importance and was not determinant for physicians and hospitals who did not prefer *Altuzan*. However, in the opinion dated 26.01.2019 quoted in paragraph 58 above and submitted by TOA to AIFD, this statement in *Altuzan's* prospectus was emphasized by underlining this statement. It was stated that by doing so, the potential risks of intraocular use were emphasized beyond being an off-label drug. In addition, in the above-mentioned answer of (.....), it was stated that the medical sales representatives implied to the physicians that the use of *Altuzan* might cause medical malpractice, based on the absence of a statement in the package insert that the product can be used intraocularly. Consequently, it is considered that the statement in *Altuzan's* SPC that it is not suitable for intravitreal use constitutes a strong example of the negative promotion pointed out by the aforementioned Hospital.

(331) The fact that the application to TMMDA regarding *Altuzan* was made by ROCHE, the license holder of the product, indicates that the violation serves to direct the relevant demand entirely to *Lucentis.* Therefore, the fact that this clearly overlaps with the interests of NOVARTIS (and ROCHE due to its indirect relationship with NOVARTIS) does not change because, in the continuation of the violation, NOVARTIS carried out negative promotional activities against the use of *Altuzan* in relevant treatments, filed a written objection to public institutions against the HIC amendment dated 28.12.2018, went to court, and participated together with the same undertakings in the relevant activities of AIFD, who represents NOVARTIS and ROCHE. In this case, it is not possible to accept that NOVARTIS is exempt from the violation, considering its financial incentives and actions taken in response to events.

(332) **The following statements in the plea: There was no evidence of an effect discouraging the institutions and physicians from the use of Altuzan in the evaluations made within the scope of the file.**

(333) The observations made regarding the presentation made in Kayseri Erciyes University and included in paragraph 38 above clearly show that NOVARTIS made negative promotions against preferring *Altuzan* for intraocular treatments.

(334) Another evidence of this is the internal correspondence of NOVARTIS cited in paragraph 37. In this document, it is stated that around 100 (boxes) of *Avastin* are used per month in Trabzon Karadeniz Faculty of Medicine, and referring to the existence of an endophthalmitis case in Mexico a question about how to share it with doctors is raised. The document dated 03.09.2015 is an example of the fact that this drug was preferred in public hospitals even in 2015, long before the HIC amendment. It is clear that NOVARTIS took a position before physicians against this.

(335) **The following statements in the plea: In the evaluations made within the scope of the file, it is claimed that the two undertakings were in concerted practice in line with a global strategy and formed a cartel by sharing the market. However, the existence of direct or indirect contact, meeting of will and parallel behavior between the parties was not demonstrated.**

(336) In the case under investigation, it is found that ROCHE was active in licensing and NOVARTIS was active in negative promotion to physicians in the case under investigation. While NOVARTIS was the party to the investigation which directly objected to SSI and TMMDA and filed a lawsuit against HIC amendment, the will of ROCHE was also represented in AIFD's initiatives. The parties to the investigation attended/involved together in many meetings and correspondence before AIFD. As a result of these findings, it is not possible to state that that ROCHE and NOVARTIS acted independently of each other in the case under investigation. In addition, a document containing trade secrets about *Lucentis*' marketing strategy was found during the on-site inspection at ROCHE. The fact that such a document related to one of the products under investigation is found in the supplier of the rival product clearly shows that the parties are in communication about the investigation. In addition, it is found that ROCHE and NOVARTIS came together regarding the case under investigation at events held within/through AIFD. It is not possible to provide a reasonable explanation for this situation from the perspective of competition law.

(337) While the chronology of the events, academic studies, and doctor practices as well as the opinions of the associations of undertakings in various countries, public regulations and court decisions promote the use of *Bevacizumab* in intraocular treatments, ROCHE's failure to actively assess its sales potential in this area is incomprehensible in terms of the strategic choices and commercial interests of an undertaking that is expected to act independently. Because for *Bevacizumab* which has a serious price advantage when compared to *Ranibizumab*, it should be expected that steps be taken to evaluate the aforementioned income potential in commercial terms whereas ROCHE acts in the opposite direction, arguing that its product is not suitable for use in related treatments, does not request the addition of these indications to the license, and does not develop single-use forms for these treatments. NOVARTIS, on the other hand, practices negative promotion about rival product *Avantis/Altuzan* before physicians and public authorities and raises objections in administrative and judicial processes. It is concluded that the mentioned actions violate Article 4 of the Act No. 4054 due to the findings made within the scope of the file that the process above took place through the joint actions of NOVARTIS and ROCHE.

(338) **The following statements in the plea: The statements in the internal document regarding the presentation made in Kayseri are in accordance with the law. The answers given to the physicians at the meeting are based on scientific studies and are not misleading.**

(339) The content of the e-mail titled "Kayseri Erciyes University *Ranibizumab* PFS presentation on safety and efficacy" sent from NOVARTIS Regional Medical Manager to NOVARTIS Regional Medical Director on 22.03.2019, obtained during on-site inspections is given above.

(340) Although the mentioned presentation is about the safety and efficacy of *Ranibizumab*, it is understood from the explanations in the document that mainly conversations about *Bevacizumab* are in the presentation. Moreover, physicians raised objections and questions that the Ministry of Health was late in the HIC amendment and they were already applying *Bevacizumab*, the treatment cost of *Ranibizumab* was very high and why *Bevacizumab*, which provides the same treatment at a much lower cost, would not be applied, the efficacy of *Bevacizumab* was almost like *Ranibizumab*, *Bevacizumab* did not show many side effects in the CATT research. Considering its efficacy, side effects and cost, it is seen that physicians who are seemingly to be in favor of the use of *Altuzan* are given negative references in terms of the adequacy of their clinical studies, efficacy, side effects and the risk of endophthalmitis. There are no references in the document to scientific publications and studies on which negative information about preference for *Altuzan* for ocular treatments is based. Only and yet again without academic reference, the DERBI study in Israel is mentioned. In addition, it is not clear where the endophthalmitis case brought by a physician, occurred, how many people it affected, and what level of vision loss it caused.

(341) In this context, it is clear that in the presentation related to *Ranibizumab* at Kayseri Erciyes University, information that may discourage the *Altuzan* preference in relevant treatments is presented rather than the promotion of *Lucentis*, and this information is not based on scientific sources.

(342) **The following statements in the plea: The document, which is stated to be found at ROCHE and contains trade secrets about marketing strategy of *Lucentis,* was not created by NOVARTIS but was issued by Genentech Inc. in the USA. It is not related to the Turkish market, but to the marketing activities of the product in the USA. The development and commercialization of *Lucentis* in the USA is the responsibility of Genentech, a subsidiary of the Roche Group. NOVARTIS has no *Lucentis*-related activities in the USA.**

(343) The Excel file found at ROCHE named “Lucentis Value Proposition Plan” includes the marketing policy of *Lucentis* sold by NOVARTIS Turkey, what kind of brand perception it will create, the scope of the value proposition campaign it will launch in April 2019, what the success metrics of the campaign are, who has which roles on duty in the campaign, the contact information of these people, which channel the target audience will be reached in marketing activities, which actions will be taken in which periods of 2019, the purpose of the brand and the messages it will give to consumers and physicians.

(344) The persons involved in the marketing activities and the information except the contact information of these persons are of interest not only to the USA but also to Turkey, contrary to the claim in the plea. Two products found to be in the same relevant product market and in competition are sold by different undertakings that do not belong to the same economic integrity. Therefore, even if these two undertakings have various connections abroad, they are competitors within the scope of Turkish structuring or in commercial transactions concerning Turkey. Thus, they should be sensitive about trade secrets.

(345) During the on-site inspection, the relevant document was found in the computer of ROCHE Marketing director, who makes the sales of *Altuzan* in Turkey. In this sense, the fact that ROCHE which sells the competing product have the trade secret document, which contains the marketing strategies for *Lucentis* product, the sales of which is made by and the license of which belongs to NOVARTIS cannot be explained by the foreign and in-group connections of the undertakings.

(346) **The following statements in the plea: NOVARTIS filed a lawsuit against the HIC amendment on its own and in line with its own independent interests. This is presented as an action restrictive of competition, although it is a constitutional right.**

(347) NOVARTIS filing a lawsuit against the HIC amendment was not considered as an issue against competition in the evaluations made within the scope of the file. In other words, it is not the parties exercising their legal rights that is considered a violation within the scope of Article 4 of Act No. 4054, but that ROCHE and NOVARTIS acted jointly and encourage the use of *Lucentis* among rival products in intraocular treatments and discourage the preference to *Altuzan*, directed/tried to direct the administration/judiciary processes with misleading information and negatively promoted Altuzan to physicians.

(348) **The following statements in the plea: BAYER and ALLERGAN were also affected by the HIC amendment and attended meetings at AIFD. In this case, the question arises as to why the undertakings in question were not included in the investigation.**

(349) In the evaluations made within the scope of the file, attending the meetings at AIFD was not considered a violation alone. In this sense, it was concluded that the parties to the investigation were not only represented by AIFD during the appeal/litigation process, but also came together at events held within or through AIFD. However, this finding alone was not put forward as evidence for the existence of a violation. What is considered a violation is that NOVARTIS and ROCHE acted jointly and deterred the use of *Altuzan* in treatments applied intraocularly by directing the administrative or judicial processes with misleading information by highlighting the risk of endophthalmitis and side effects of *Altuzan*, in a way that will shift the demand to *Lucentis*, that the aforementioned undertakings created a perception of difference that *Altuzan* and *Lucentis* are different, which did not reflect the truth, and in this context, made negative promotion about *Altuzan* to physicians.

(350) **The following statements in the plea: While BAYER and NOVARTIS took action against the HIC amendment, AIFD and ROCHE did not prefer to do so. In this case, those concerned did not act in parallel after the AIFD meetings. Showing the participation of ROCHE and NOVARTIS in AIFD meetings as a harmony of will is a contrived argument.**

(351) The position taken by AIFD against the HIC amendment, the relationship of the parties to the investigation with AIFD and their participation in the relevant correspondence and meetings together during this process, and how these were handled in terms of violation assessment are explained above. On the other hand, it is clear that the HIC amendment dated 28.12.2018 is directly related to *Eylea's* license holder BAYER, and the steps of this undertaking in appealing to public institutions and taking legal action can be explained by commercial incentives. However, the evaluations made in the licensing and promotion side of the violation, the existence of which is evaluated within the scope of the investigation, are ROCHE and

NOVARTIS oriented. More importantly, the license agreement for *Lucentis* between GENENTECH, a subsidiary of the Roche Group, and NOVARTIS enables ROCHE to indirectly generate revenue from each box of *Lucentis* sold, in addition to fixed income, in Turkey and elsewhere. Therefore, this situation creates a conflict of interest between the parties and eliminates the incentive to evaluate the sales potential of *Altuzan* in ocular treatments, which could steal from ROCHE's *Lucentis* sales. Since it is obviously in favor of NOVARTIS, there is no need for an analysis of anticompetitive gains created by this relationship for the aforementioned undertaking. In this context, it is unnecessary to question why ROCHE and NOVARTIS are held responsible in terms of the activities carried out by AIFD.

(352) A brief explanation was made regarding the status of ROCHE in terms of AIFD meetings/correspondence and whether this differs from the relevant will of NOVARTIS.

(353) As mentioned above, the e-mails of AIFD Market Access and Health Policy Directors, dated respectively 03.01.2019, 28.01.2019 and 28.02.2019 were sent to ALLERGAN, BAYER and NOVARTIS as well as to ROCHE. As stated before, there is no evidence that ROCHE, whom NOVARTIS stated that “appears” to be passive, made a statement or stance to stay out of events and conversations carried out by AIFD related to the subject of investigation. Therefore, ROCHE contributed to the will formed in meetings and relevant correspondences within AIFD both as a director and as a member. In this case, contrary to what is claimed in the plea, it is not possible to argue that ROCHE followed a different stance from AIFD and NOVARTIS on the objection to the HIC amendment.

(354) **The following statements in the plea: The statement that the meetings at AIFD were held regarding the use of *Altuzan* in intraocular treatments is false/misleading. The meetings were about the acceptance of an off-label drug as mandatory first-line treatment while a licensed product is available.**

(355) It is clear that the main purpose of the relevant argument is to decouple the meetings and correspondence held under the organization of AIFD from the subject of the investigation. According to the plea, these meetings (and correspondence) were not held on *Altuzan's* use in ocular treatments or limited to its use, though it was not stated in such a way.

(356) Relevant meetings were held before and after the HIC amendment dated 28.12.2018. The meetings formed the background for obtaining results before the public institutions regarding the said regulation and then going to the judiciary. The Communiqué amendment, which is the subject of objections and lawsuits, stipulates that the use of *Bevacizumab* in intraocular treatments is required under certain conditions. The drug containing *Bevacizumab* licensed in Turkey is *Altuzan* and this product is used off-label in relevant treatments. Therefore, the meetings were held on the discretion of SSI and TMMDA regarding the mentioned use of *Altuzan*. The fact that the subject of the meeting was expressed in a different way does not change this fact and does not undermine the observations made within the scope of the file.

(357) On the other hand, making *Altuzan* mandatory in first-line treatment is a regulation in favor of ROCHE. While the HIC amendment encouraged the use of *Bevacizumab* in intraocular treatments, ROCHE’s failure to actively assess its sales potential in this area is incomprehensible in terms of the strategic choices and commercial interests of an undertaking that is expected to act independently.

(358) It is intended to create the impression that AIFD meetings are held at a principled level in the plea. However, as mentioned above, the e-mails of AIFD Market Access and Health Policy Directors, dated respectively 03.01.2019, 28.01.2019 and 28.02.2019 were sent to ALLERGAN, BAYER and NOVARTIS as well as to ROCHE. It is noteworthy that these correspondences were not with all AIFD members, but with undertakings whose sales would be directly affected by the HIC amendment, and that ROCHE was involved in these correspondences together with pharmaceutical companies with which it is involved in a conflict of interest.

(359) **The following statement in the plea: While there were no observations against *Lucentis* in the endophthalmitis case in Van, the court decision and the Forensic report, the endophthalmitis risk was equal for *Altuzan* and *Lucentis* from the point of view of this case.**

(360) Following the reference to the decision of the Van 1st Administrative Court, No. 2017/2179 E. and 2020/335 K., the statement *"Undoubtedly, the Investigation Committee is in no position to open the safety of Ranimizumab to discussion based on this decision. However, the case which is the subject of the court decision shows that intraocular use of anti-VEGF agents always poses certain levels of risk and that this is not only valid for Altuzan, for example negative consequences may occur when Ranibizumab is used. However, while the parties to the investigation, relevant undertakings and associations frequently referred to the endophthalmitis case in Kırıkkale University Faculty of Medicine, the case which occurred after Ranibizumab injection and resulted in permanent vision loss in Van was never mentioned. This is considered to be an extension of the strategy of disseminating misleading information to physicians, public institutions and the public opinion."* clearly shows that the argument is not valid.

(361) Based on the Van case in the evaluations made within the scope of the file, the safety of *Ranimizumab* was not open to discussion. It shows that the intraocular administration of anti-VEGF agents always involves certain levels of risk, and that this is not valid only for *Altuzan*, the use of *Ranibizumab* may also have negative outcomes. As a result, various risks may arise in the use of both *Altuzan* and *Lucentis*, there is not a conclusion that using *Altuzan* does not lead to risks. Only the similarities of the *Altuzan* cases in Kırıkkale and *Lucentis* cases in Van were mentioned.

(362) Infact, the lawsuit filed at a later date by a patient who was administered *Ranibizumab* on 21.12.2016 was examined by the court[84], and an expert witness was first consulted within the scope of the file. The statements in the expert report dated 11.02.2019 are: Endophthalmitis developed a day after the procedure. The report dated 27.12.2016 showed that there was a *rhizobiumradiobacter* bacterial growth in the patient. Appropriate treatment for endophthalmitis was applied in the hospital and the treatment applied was in accordance with the general principles of medical management. However, considering that endophthalmitis was detected consecutively in other patients treated on the same date in the relevant file, it was mentioned that the developing infection was transmitted from an undetected source in the hospital and resulted from sterilization conditions. Using the expert report in question, the court concluded that the endophthalmitis, which is the subject of the case, was caused by the surgical and sterilization conditions, and that there was a malpractice due to the

[84] Decision of Van 3rd Administrative Court dated 19.06.2020 and numbered E. 2017/2628 K. 2020/2156.

poor execution of the health service and concluded that compensation shall be paid to the complainant by the administration.

(363) In this respect, both *Altuzan* and *Lucentis* may cause endophthalmitis when applied to the patient under unsuitable sterilization conditions.

(364) **The following statements in the plea: The views of TOA, physicians and hospitals obtained within the scope of the file were not taken into consideration in the evaluation.**

(365) Contrary to the claim, the aforementioned views were taken into consideration and influenced the evaluation. According to the information obtained from the hospitals, while *Lucentis* was the most used drug in the treatment of said diseases before the HIC amendment in most of the hospitals, the rates of *Altuzan* usage increased after the HIC amendment. In addition, it seems that the physicians became concerned about their own actions being the subject of such lawsuits after they heard the medical malpractice lawsuits filed against their colleagues who applied *Altuzan* to patients. Therefore, it seems that the negative promotions about *Altuzan* have affected the physicians.

(366) On the other hand, views and statements that support the arguments in the plea are included, even if they are not compatible with the conclusion reached in the decision. For example, in the relevant product market section, ROCHE's statements on the subject are given under a separate heading. Thus, the views that do not support the conclusion reached are also shared in the decision. However, even in the written responses which the party considers to be in their favor, information confirming the findings reached within the scope of the file is included, but it is noteworthy that these are not mentioned in the plea. The hospital responses that are among the documents which are said to be ignored in the evaluation section are as follows:

- *Altuzan* was preferred before the HIC amendment at (.....), for diseases and in some rare cases where anti-VEGF must be used.

- *Altuzan* was applied in cases where licensed drugs could not be used in indications of *Lucentis* and *Eylea*, and *Altuzan* was used at a (.....)% rate before the HIC amendment at (.....).

- The usage patterns, application doses and frequencies of *Altuzan*, *Lucentis* and *Eylea* are similar. At (.....), *Altuzan* was preferred at a rate of (.....)% -ranking first by far in the relevant treatments-. In 2020, this product was used at a rate of (.....)%, while it ranks first by far although the rate has decreased.

- *Altuzan* was preferred at (.....) at a rate of (.....)% –ranking first by far – before and after the HIC amendment.

- Before the HIC amendment, some patients took *Altuzan* which is more affordable together with other patients and had it applied in some health centers. With the emphasis that applying a vial to more than one patient may increase the risk of infection; it is demonstrated by publications and clinical experience that *Bevacizumab* is as effective as other drugs with indications for intraocular applications in the world and in Turkey.

- *Altuzan* is one of the products used in relevant treatments. At (.....), *Altuzan* was applied at a rate of (.....)%, ranking first by far, prior to the HIC amendment, and physicians relied on *Altuzan's* efficacy despite concerns that *Altuzan*

use could raise the issue of malpractice suits.

- *Altuzan* has been used off-label in relevant treatments and in rare cases with similar pathology. *Altuzan* was preferred at (.....) at a rate of (.....)% in the relevant treatments before the HIC amendment.

(367) **The following statement in the plea: The Competition Authority does not have the competence and power in medical matters such as the use of licensed and off-label drugs.**

(368) Parallel to this argument, the investigation in the file was carried out in close cooperation with institutions and organizations such as SSI, TMMDA, hospitals, with the awareness that there is no competence in scientific fields related to medical issues, except for the dimensions of competition law and regulations related to competition law. In the light of information and documents regarding medical issues compiled from a wide variety of sources, individuals and institutions, attention is paid to make evaluations only related to the competition law.

(369) **The following statement in the plea: The obscuration of some information in the Investigation Report and the rejection of the request for access to the file for some documents restrict the party's right of defense.**

(370) Although undertakings have the right to request information/documents related to them within the scope of the investigation, it is essential that access to these information/documents be made to the extent permitted by the provisions of the legislation. In this context, it can be stated that Article 6 of the Communiqué No. 2010/3 draws the said limit. Pursuant to the said provision, the parties are able to access all kinds of documents and all kinds of evidence obtained within the Authority, with the exception of internal correspondence, trade secrets and other confidential information. Access to such documents, which constitute an exception to the right of access to the file, is prohibited as a rule. Prohibition of access to documents found to be of this nature will not be considered as a restriction of the right of defense. The attorney of the undertaking exercised the right of access to the file in accordance with the relevant legislation. The right of defense of the undertaking was not restricted, on the contrary, by opening the correspondence with many public institutions and organizations to the access of the representative of the undertaking in the Authority building, the undertaking had the opportunity to prepare a plea regarding the relevant documents.

(371) **The following statement in the plea: The Court in Rome recently ruled to the contrary of the ICA decision and dismissed the criminal case brought against the management of Italian companies based on similar facts as unfounded.**

(372) A decision of the Roman Court was included within the scope of the plea, but the said decision could not be reached since information such as which court, date, number and access address was not provided.

(373) **The following statement in the plea: It was stated that AIFD's demand for an opinion from TOA was due to the request of ROCHE. However, this was done with the decision of the board of directors of AIFD (Document 66/3).**

(374) The statement that the meeting was at the request of ROCHE was written inadvertently. However, since no violation is detected based on this information, the

assessment made, and the conclusion reached will not change.

I.4.4. Evaluation Regarding the Administrative Fee

I.4.4.1. The Severity of the Violation

(375) The third paragraph of Article 16 of the Act No. 4054 states*, "To those who commit behavior prohibited in Articles 4, 6 and 7 of this Act, an administrative fine shall be imposed up to ten percent of annual gross revenues of undertakings and associations of undertakings or members of such associations to be imposed a penalty, generated by the end of the financial year preceding the decision, or generated by the end of the financial year closest to the date of the decision if it would not be possible to calculate it and which would be determined by the Board."* According to this provision, it is considered that an administrative fine shall be applied to ROCHE and NOVARTIS, which are considered to have engaged in prohibited behavior in Article 4 of Act No. 4054.

(376) The fifth and last paragraphs of Article 16 of the Act No. 4054 are as follows: *"When deciding on an administrative fine pursuant to paragraph three, the Board shall take into consideration issues such as the repetition of infringement, its duration, market power of undertakings or associations of undertakings, their decisive influence in the realization of infringement, whether they comply with the commitments given, whether they assist with the examination, and the severity of damage that takes place or is likely to take place, within the context of Article 17 paragraph two of the Law of Misdemeanors dated 30/3/2005 and numbered 5326."* and *"To those undertakings or associations of undertakings or their managers and employees making an active cooperation with the Authority for purposes of revealing violations of the Act, penalties mentioned in paragraphs three and four may not be imposed or reductions may be made in penalties to be imposed pursuant to such paragraphs taking into consideration the quality, efficiency and timing of cooperation and by means of demonstrating its grounds explicitly."*

(377) According to Article 5 of the Regulation on Fines which was issued in order to regulate the procedures and principles regarding the administrative fine in accordance with Article 16 of the Act to be given to those who perform the prohibited acts in Articles 4 and 6, the basic fine is calculated and then the aggravating and mitigating factors according to articles 6 and 7 are considered.

(378) In order to determine the basic fine, whether the violation is a cartel or not must first be evaluated. In Article 3 (d) of the Regulation on Fines, the cartel is defined as *"competition restrictive agreements and/or concerted practices between competitors for fixing prices; allocation of customers, providers territories or trade channels; restricting the amount of supply or imposing quotes and bid rigging."*

(379) With this violation detected within the scope of the file, the undertakings who are parties to the investigation aimed to shift the demand in the market of "intraocularly applied anti-VEGF molecules" to *Lucentis* by acting jointly, by disseminating misinformation to various public institutions and organizations, physicians, and associations of undertakings in order to increase the concerns about the use of *Altuzan.* Considering this aspect, it is seen that selling *Lucentis* to patients who need intraocularly applied anti-VEGF molecules in their treatment will serve the common interests of the parties. On the other hand, it is understood that prescribing *Altuzan*, which is much more affordable than *Lucentis*, does not serve the common interest of the parties. Therefore, there were attempts to suppress the sales of *Altuzan*

and discourage the use of *Altuzan* as an intraocularly applied anti-VEGF molecule by the joint will of the parties. In other words, the market for intraocularly applied anti-VEGF molecules is left to NOVARTIS with the joint will of the parties for the common interest of the parties. Thus, there was an attempt to use *Altuzan* only in oncological treatments and preventing it from entering to *Lucentis'* market.

(380) This market-sharing by the parties to meet the demand for intraocularly applied anti-VEGF molecules with higher-priced Lucentis increases public spending without improving treatment or increasing efficacy. On the other hand, it also causes disadvantages for patients who are ultimate consumers, as physicians who are concerned about Altuzan's risks direct their patients to get Lucentis, which is provided by the patient share, instead of Altuzan which is currently exempt from the patient share.

(381) In this context, the conclusions are as follows: The act under investigation resembles the allocation of a product market example, and in this respect, restricts competition. In addition, due to the attempt of shifting the demand for intraocularly applied anti-VEGF molecules to *Lucentis*, customers who were essentially buyers of these molecules shifted to *Lucentis*. The public institutions and organizations as well as physicians who create the demand were misinformed about *Altuzan*, and as a result, the intraocularly applied anti-VEGF molecules market and therefore indirectly the customers in this market were shared. Consequently, this reduces the options for consumers and the public and causes financial damages. Therefore, the afore-mentioned actions are in line with the definition of cartel in subparagraph (d) of Article 3 of the Regulation on Fines and benefitting from the exemption under Article 5 of the Act No. 4054 is not possible.

I.4.4.2. The Power of the Relevant Undertakings on the Market and the Gravity of the Possible Loss

(382) It is regulated in the second paragraph of Article 5 of the Regulation on Fines that in determining the basic fine, the power of the relevant undertakings in the market and the gravity of the possible loss as a result of the violation of the relevant undertakings will be taken into account.

(383) Anti-VEGF agents that can be used in intraocular treatments are *Bevacizumab*, *Ranibizumab* and *Aflibercept*. The relevant products used in these treatments in Turkey are *Altuzan*, *Lucentis* and *Eylea*. According to the quantitative (box) data obtained from IQVIA, while the market leader in 2016 and 2017 was *Lucentis*, *Eylea* became the new leader with the rapid rise in sales in 2018. The share of *Lucentis* in the relevant market was close to (.....)% in 2018. Due to the fact that IQVIA data did not contain the breakdown of indication, it was not possible to calculate how much the total amount of *Altuzan* sold was used in intraocular treatments. Therefore, there was not a definite calculation in 2019. However, it is possible to state that in 2019, the share of this product in the relevant market was at high levels following the regulation about its mandatory use in the first line treatment.

(384) The findings regarding the market power of the parties in the relevant market also explain the severity of the loss caused by the violation. In addition, the reimbursement amounts of the SSI in relevant treatments decreased by 22.4% of after the use of *Altuzan* was made mandatory in first-line treatments with the HIC amendment dated 28.12.2018. This should be evaluated within this framework. In other words, by discouraging the use of *Altuzan*, which is cheaper compared to *Lucentis*, in intraocular treatments, the ability of the state to make significant savings

is eliminated. Therefore, the financial load on the patients due to the patient share was not mitigated.

I.4.4.3. The Duration of the Violation

(385) According to the third paragraph of Article 5 of the Regulation on Fines, the basic fine may be increased according to the duration of the violation. The assessment on the duration of the violation is given below.

(386) Considering the dates when *Altuzan (Avastin)* and *Lucentis* were licensed, included in the reimbursement and put on the market in other countries and in Turkey, and the periods examined by the ICA and the CJEU, it is possible to state that the beginning of the concerted behavior under investigation has a long history. However, in terms of the file in question, it is clear that a reference shall be specified according to the legally indisputable and concrete cases. According to the documents at hand, the first concrete step for ROCHE and NOVARTIS to highlight *Lucentis* among the rival drugs used in relevant treatments was ROCHE's application to TMMDA to add the phrase "*Altuzan* is not suitable for intravitreal use." to *Altuzan's* SPC and PIL. As stated in the section where the SPC/PIL amendment process is explained in detail, ROCHE made the first applications for the 100 mg and 400 mg forms of *Altuzan* on 29.12.2011. Accordingly, it is accepted that the violation started as of 29.12.2011.

(387) After the HIC amendment (Article 4.2.33) dated 28.12.2018 and the 2019 amendment of *Altuzan's* SPC/PIL, the actual consequences of the concerted behavior, which is considered to be within the scope of Article 4 of the Act No. 4054, have largely disappeared. These two processes are considered as a whole. On the one hand, while the use of *Becavizumab* is made mandatory in the first-line treatment of ocular diseases listed in subparagraphs (A), (B), (C) and (Ç) of the article 4.2.33 of the HIC and this practice is exempted from the patient share, on the other hand, the statements that *Altuzan* is not suitable for intraocular use and other relevant statements are removed from *Altuzan's* SPC/PIL. It is possible to observe the concrete results of these developments. The following tables show the analysis using data from IQVIA.

Table 4- Annual Sales of 100 mg 4 ml form of Altuzan between 2016 and 2019 (Box)

	2016	2017	2018	2019
Retail Pharmacy	(.....)	(.....)	(.....)	(.....)
Hospital	(.....)	(.....)	(.....)	(.....)
Total	(.....)	(.....)	(.....)	(.....)
Increase Compared to Previous Year (Retail Pharmacy)	(.....)	(.....)	(.....)	(.....)
Increase Compared to Previous Year (Hospital)		(.....)	(.....)	(.....)
Increase Compared to Previous Year (Total)		(.....)	(.....)	(.....)
Source: The Response of IQVIA				

Table 5- Monthly Sales of 100 mg 4 ml form of Altuzan between 2016-2019 (Box)

	Retail	Hospital	Total
2016 Monthly Average	(.....)	(.....)	(.....)
2017 Monthly Average	(.....)	(.....)	(.....)
2018 Monthly Average	(.....)	(.....)	(.....)
2019 January	(.....)	(.....)	(.....)
2019 February	(.....)	(.....)	(.....)
2019 March	(.....)	(.....)	(.....)
2019 April	(.....)	(.....)	(.....)
2019 May	(.....)	(.....)	(.....)
2019 June	(.....)	(.....)	(.....)
2019 July	(.....)	(.....)	(.....)
2019 August	(.....)	(.....)	(.....)
2019 September	(.....)	(.....)	(.....)
2019 October	(.....)	(.....)	(.....)
2019 November	(.....)	(.....)	(.....)
2019 December	(.....)	(.....)	(.....)
2019 Monthly Average	(.....)	(.....)	(.....)
Source: The Response of IQVIA			

(388) Hospital pharmacies provide 100 mg form of *Altuzan* for intraocular treatments. If not available at the hospital pharmacy, the drug can be purchased from retail pharmacies. Therefore, the sales of the drug in question in both channels were examined both separately and together.

(389) Considering the annual sales of the 100 mg form of *Altuzan* during the period between 2016-2019, the jump in 2019 is noteworthy. In the hospital channel, which is the main supply route for the drug, there was a (.....) increase in 2019 compared to the previous year. Taking a look at the monthly sales of the same drug, according to the average monthly sales ((.....), (.....), (.....)) for 2016-2017-2018, the average monthly sales for 2019 reaching (.....) is noticeably high. Considering the fact that the HIC amendment entered into force at the end of January 2019, it seems that monthly sales had been at a high level, especially since March 2020. The average sales, which reached (.....) in the specified 10 months, is also above the amount in 2019. On the other hand, there is a similar situation in terms of monthly sales in the hospital channel, which is the main supply route of the drug in relevant treatments.

(390) The information included in the written statement of the SSI also confirms the findings that the HIC amendment dated 28.12.2018 caused an increase in the sales of Altuzan. According to the MEDULA System records, the number of patients who used Altuzan in intraocular treatments increased by (.....)% and the reimbursement amount for Altuzan increased by (.....)% in 2019. Also, according to said records, due to the increase in the use of Altuzan, the number of patients treated with Eylea and Lucentis respectively decreased by (.....)% and (.....)%, and the reimbursement amount for the same drugs decreased by (.....)% and (.....)%. Consequently, the rate of the savings achieved in public drug expenditures in related

treatments were 22.4%. Data from IQVIA also reveals that sales of Eylea and Lucentis decreased, whereas sales of Altuzan increased in 2019.

(391) The increase in sales caused due to the use of Altuzan in intraocular treatments shows that the HIC amendment dated 28.12.2018 has largely eliminated the economic impact of the violation for the public and patients. In the pillar of the violation concerning promotion to physicians, it was not possible to make clear determinations. However, considering the responses of the hospitals, the concern that physicians may be the subject of lawsuits in undesirable situations that may arise during Altuzan applications, and may also be possible regarding other anti-VEGF drugs, as in the case of Van, shows that the effects of negative promotions continue. However, there are not any findings that the activities aiming to discourage preferring *Altuzan* and directing the demand to *Lucentis* are carried out actively at present.

(392) The administrative process took some more time to end in terms of licensing. The process, which started with the letter of TMMDA dated 05.11.2018, with the request to remove the phrase in *Altuzan's* SPC and PIL stating that the drug is not suitable for intravitreal use, was concluded with the approval of the amendment of this statement by TMMDA on 10.05.2019 as in the original reference document. Between 05.11.2018 and 10.05.2019, there were many correspondences between TMMDA and ROCHE. However, ROCHE did not want to fulfill the request of TMMDA, but the problem was resolved when the suspension of the product's license might be possible. ROCHE made the application on 15.03.2019, which ended with the approval of TMMDA dated 10.05.2019. Therefore, it is accepted that the will of the party with respect to licensing ended on the specified date.

(393) Another aspect that constitutes the scope of the violation is that NOVARTIS made negative promotions of its rival product *Avastin/Altuzan* to the physicians and public authorities. It seems that these activities continued after the amendments in licensing. In this context, the contents of the e-mail titled “Kayseri Erciyes University *Ranibizumab* PFS presentation on safety and efficacy" sent from NOVARTIS Regional Medical Manager to NOVARTIS Regional Medical Director on 22.03.2019 is noteworthy. It is understood from the e-mail in question that the information that may discourage *Altuzan* preference in relevant treatments was presented in the presentation made at Kayseri Erciyes University, related to *Ranibizumab* and this information was not based on scientific sources. As stated in the relevant section, the document clearly shows that NOVARTIS made negative promotions against *Altuzan* preference in intraocular treatments. In this context, the date of the e-mail in question, 22.03.2019, was taken as the ending date of the violation.

(394) As a result, the starting and ending dates that may be taken as reference in terms of determining the duration of the violation are 28.12.2011 and 22.03.2019, therefore, it is concluded that the violation lasted longer than seven years.

I.4.4.4. Mitigating Factors

(395) The mitigating factors specified in the first paragraph of Article 7 of the Regulation on Fines are not applicable for the file.

(396) Considering the issues mentioned above, the rate for the basic fine for NOVARTIS and ROCHE, who are found to have violated Article 4 of the Act No. 4054, is determined as (….)% in accordance with the third paragraph of Article 16 of the Act No. 4054 and the subparagraph (a) of the first paragraph and the second paragraph

of Article 5 of the Regulation on Fines. On the other hand, the duration of the mentioned violation is determined to be longer than five years, and the rate based on the calculated basic fine is increased by one fold in accordance with subparagraph (b) of the third paragraph of Article 5 of the Regulation on Fines, and is calculated as (.....)%.

J. CONCLUSION

(397) According to the Report, the Additional Opinion, the evidence collected, written pleas, the explanations made during the oral hearing and the scope of the file examined regarding the investigation conducted per the Board decision dated 13.06.2019 and numbered 19-21/307-M, it was decided UNANIMOUSLY that

1- Novartis Sağlık Gıda ve Tarım Ürünleri San. ve Tic. A.Ş. and Roche Müstahzarları San. A.Ş. violated Article 4 of Act No. 4054,

2- Therefore, according to third paragraph of Article 16 of the Act No. 4054 and Article 5(1)(a), 5(2) and 5(3)(b) of "the Regulation on Fines to Apply in cases of Agreements, Concerted Practices and Decisions Limiting Competition, and Abuse of Dominant Position", amounting to (.....)% of the annual gross revenues which generated at the end of the financial year 2019 and which is determined by the Board, by discretion

- Novartis Sağlık Gıda ve Tarım Ürünleri San. ve Tic. A.Ş. shall be imposed 165.464.716,48 TL administrative fines

- Roche Müstahzarları San. A.Ş. shall be imposed 112.972.552,65 TL administrative fines.

The decision can be appealed before Ankara Administrative Courts within 60 days as of the notification of the reasoned decision.