Reports of Cases

JUDGMENT OF THE COURT (Grand Chamber)

23 January 2018*

(Reference for a preliminary ruling — Competition — Article 101 TFEU — Agreements, decisions and concerted practices — Medicinal products — Directive 2001/83/EC — Regulation (EC) No 726/2004 — Allegations of risks associated with the use of a medicinal product for a treatment not covered by its marketing authorisation (off-label) — Definition of relevant market — Ancillary restriction — Restriction of competition by object — Exemption)

In Case C-179/16,

REQUEST for a preliminary ruling under Article 267 TFEU from the Consiglio di Stato (Council of State, Italy), made by decision of 3 December 2015, received at the Court on 25 March 2016, in the proceedings

F. Hoffmann-La Roche Ltd,

Roche SpA,

Novartis AG,

Novartis Farma SpA

v

Autorità Garante della Concorrenza e del Mercato,

intervening parties:

Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds),

Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI),

Regione Emilia-Romagna,

Altroconsumo,

Regione Lombardia,

Coordinamento delle associazioni per la tutela dell'ambiente e dei diritti degli utenti e consumatori (Codacons),

Agenzia Italiana del Farmaco (AIFA),

* Language of the case: Italian.

THE COURT (Grand Chamber),

composed of K. Lenaerts, President, A. Tizzano, Vice-President, R. Silva de Lapuerta, M. Ilešič, J. Malenovský, C.G. Fernlund (Rapporteur) and C. Vajda, Presidents of Chambers, A. Borg Barthet, J.-C. Bonichot, A. Arabadjiev, F. Biltgen, K. Jürimäe and C. Lycourgos, Judges,

Advocate General: H. Saugmandsgaard Øe,

Registrar: R. Schiano, Administrator,

having regard to the written procedure and further to the hearing on 3 May 2017,

after considering the observations submitted on behalf of:

– F. Hoffmann-La Roche Ltd, by M. Siragusa, P. Merlino and G. Faella, avvocati,

– Roche SpA, by E. Raffaelli, P. Todaro, A. Raffaelli and E. Teti, avvocati,

– Novartis AG and Novartis Farma SpA, by G.B. Origoni della Croce, A. Lirosi, P. Fattori, L. D'Amario and S. Di Stefano, avvocati,

– the Autorità Garante della Concorrenza e del Mercato, by P. Gentili, avvocato dello Stato,

– the Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds), by G. Muccio and G. Zaccanti, avvocati,

– Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI), by R. La Placa and V. Vulpetti, avvocati,

– Altroconsumo, by F. Paoletti, A. Mozzati and L. Schiano di Pepe, avvocati,

– the Coordinamento delle associazioni per la tutela dell'ambiente e dei diritti degli utenti e consumatori (Codacons), by C. Rienzi, G. Giuliano and S. D'Ercole, avvocati,

– the Regione Emilia-Romagna, by M.R. Russo Valentini and R. Bonatti, avvocati,

– the Italian Government, by G. Palmieri, acting as Agent, and S. Fiorentino, avvocato dello Stato,

– Ireland, by E. Creedon, L. Williams and A. Joyce, acting as Agents, and M. Gray, Barrister,

– the French Government, by D. Colas, D. Segoin and J. Bousin, acting as Agents,

– the European Commission, by T. Vecchi, F. Castilla Contreras, G. Conte and C. Vollrath, acting as Agents,

after hearing the Opinion of the Advocate General at the sitting on 21 September 2017,

gives the following

Judgment

1 This request for a preliminary ruling concerns the interpretation of Article 101 TFEU.

2 The request has been made in proceedings between F. Hoffmann-La Roche Ltd ('Roche'), Roche SpA ('Roche Italia'), Novartis AG and Novartis Farma SpA ('Novartis Italia'), of the one part, and the Autorità Garante della Concorrenza e del Mercato (the Italian competition authority, Italy; 'the AGCM'), of the other part, regarding the proceedings brought and the financial penalties imposed by the latter because of an agreement contrary to Article 101 TFEU.

Legal context

3 Penalties were imposed by the AGCM on the undertakings at issue in the main proceedings for infringement of EU competition law during the period between 1 June 2011 and 27 February 2014.

Directive 2001/83/EC

4 In view of the infringement period in question, the present case is governed by the provisions of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ 2001 L 311, p. 67), as amended by Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 (OJ 2007 L 324, p. 121) ('Directive 2001/83'), and, as from 21 July 2012, by the provisions of Directive 2001/83, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 74) ('amended Directive 2001/83').

5 Article 5(1) of Directive 2001/83 provides:

'A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.'

6 Under Article 6(1) of the directive:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation [('MA')] has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use [(OJ 2006 L 378, p. 1)] and Regulation (EC) No 1394/2007.

When a medicinal product has been granted an initial [MA] in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial [MA]. All these [MAs] shall be considered as belonging to the same global [MA]...'

7 Article 40(1) and (2) of the directive provides:

'1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorisation. This manufacturing authorisation shall be required notwithstanding that the medicinal products manufactured are intended for export.

2. The authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorisation shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes.'

8 Article 101(1) of amended Directive 2001/83 provides:

'Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the [MA] as well as from use outside the terms of the [MA], and to adverse reactions associated with occupational exposure.'

9 Under Article 106a of amended Directive 2001/83:

'1. As soon as the [MA] holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the [European Medicines Agency (the EMA)] and the Commission.

The [MA] holder shall ensure that information to the public is presented objectively and is not misleading.

2. Unless urgent public announcements are required for the protection of public health, the Member States, the [EMA] and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the [EMA] shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the [EMA], the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the [EMA], provide advice on those safety announcements.

…'

Regulation (EC) No 726/2004

10 In view of the infringement period in question, the present case is governed by the provisions of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ 2004 L 136, p. 1), as amended by Regulation (EC) No 219/2009 of the European Parliament and of the Council of 11 March 2009 (OJ 2009 L 87, p. 109) ('Regulation No 726/2004'), and, as from 2 July 2012, by the provisions of Regulation No 726/2004, as amended by Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 1, and Corrigendum OJ 2012 L 201, p. 138) ('amended Regulation No 726/2004').

11 Under Article 16 of Regulation No 726/2004:

'1. After an authorisation has been granted in accordance with this Regulation, the holder of the [MA] for a medicinal product for human use shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h) of Directive 2001/83/EC, take account of technical and scientific progress and make any variations that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of such variations in accordance with this Regulation.

2. The holder of the [MA] shall forthwith supply to the [EMA], to the Commission and to the Member States any new information which might entail the variation of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11 of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, he shall forthwith inform the [EMA], the Commission and the Member States of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned.

In order that the risk-benefit balance may be continuously assessed, the [EMA] may at any time ask the holder of the [MA] to forward data demonstrating that the risk-benefit balance remains favourable.

3. If the holder of the authorisation for a medicinal product for human use proposes to make any variation of the particulars and documents referred to in paragraph 2, he shall submit the relevant application to the [EMA].

4. The Commission shall, after consulting the [EMA], adopt appropriate provisions for the examination of variations to [MAs] in the form of a regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).'

12 Article 16 of amended Regulation No 726/2004 provides:

'1. After a[n MA] has been granted in accordance with this Regulation, the [MA] holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of corresponding variations in accordance with this Regulation.

2. The [MA] holder shall forthwith provide the [EMA], the Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Article 10, 10a, 10b and 11, or Article 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, the [MA] holder shall forthwith inform the [EMA] and the Commission of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the [MA], as well as data on the use of the medicinal product where such use is outside the terms of the [MA].

3. The [MA] holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26.

3a. In order to be able to continuously assess the risk-benefit balance, the [EMA] may at any time ask the [MA] holder to forward data demonstrating that the risk-benefit balance remains favourable. The [MA] holder shall answer fully and promptly any such request.

The [EMA] may at any time ask the [MA] holder to submit a copy of the pharmacovigilance system master file. The [MA] holder shall submit the copy at the latest seven days after receipt of the request.

4. The Commission shall, after consulting the [EMA], adopt appropriate provisions for the examination of variations to [MAs] in the form of a regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).'

13 Article 17 of Regulation No 726/2004 reads as follows:

'The applicant or the holder of a[n MA] shall be responsible for the accuracy of the documents and of the data submitted.'

14 Article 22 of that regulation provided:

'The [EMA], acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 102 of Directive 2001/83/EC, shall receive all relevant information concerning suspected adverse reactions to medicinal products for human use which have been authorised by the Community in accordance with this Regulation. Where appropriate, the Committee for Medicinal Products for Human Use shall, in accordance with Article 5 of this Regulation, draw up opinions on the measures necessary. These opinions shall be made publicly accessible.

…

The holder of the [MA] and the competent authorities of Member States shall ensure that all relevant information concerning suspected adverse reactions to the medicinal products authorised under this Regulation are brought to the attention of the [EMA] in accordance with the provisions of this Regulation. Patients shall be encouraged to communicate any adverse reaction to healthcare professionals.'

15 Article 24(5) of Regulation No 726/2004 stated:

'The holder of a[n MA] may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised medicinal product without giving prior or simultaneous notification to the [EMA].

In any case, the [MA] holder shall ensure that such information is presented objectively and is not misleading.

Member States shall take the necessary measures to ensure that a[n MA] holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.'

16 Pursuant to Regulation No 1235/2010, Chapter 3 of Title II of Regulation No 726/2004, that chapter being headed 'Pharmacovigilance' and comprising Articles 21 to 29 of the regulation, was replaced. Article 28(4) of amended Regulation No 726/2004 is worded as follows:

'In the case of an assessment report that recommends any action concerning the [MA], the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the [MA] concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

Where the opinion states that regulatory action concerning the [MA] is necessary, the Commission shall adopt a decision to vary, suspend or revoke the [MA]. Article 10 of this Regulation shall apply to the adoption of that decision. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.'

17 Article 84 of the regulation provides:

'1. Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for infringement of the provisions of this Regulation or the regulations adopted pursuant to it and shall take all measures necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.

…

2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.

3. At the [EMA]'s request, the Commission may impose financial penalties on the holders of [MAs] granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down by the Commission. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

The Commission shall publish the names of the [MA] holders involved and the amounts of and reasons for the financial penalties imposed.'

Regulation (EC) No 658/2007

18 In view of the infringement period in question, the present case is governed by the provisions of Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with MAs granted under Regulation No 726/2004 (OJ 2007 L 155, p. 10), and, as from 2 July 2012, by the provisions of that regulation as amended by Commission Regulation (EU) No 488/2012 of 8 June 2012 (OJ 2012 L 150, p. 68) ('amended Regulation No 658/2007').

19 Article 1(1) of Regulation No 658/2007 provided:

'This Regulation lays down rules concerning the application of financial penalties to the holders of [MAs], granted under Regulation (EC) No 726/2004, in respect of infringements of the following obligations, in cases where the infringement concerned may have significant public health implications in the Community, or where it has a Community dimension by taking place or having its effects in more than one Member State, or where interests of the Community are involved:

1. the completeness and the accuracy of the particulars and documents contained in an application for [MA] under Regulation (EC) No 726/2004, or of any other documents and data submitted to the [EMA] established by that Regulation, hereinafter "the Agency", in response to obligations laid down in that Regulation'.

20 Article 1(1) of amended Regulation No 658/2007 is worded as follows:

'the obligation to submit complete and accurate particulars and documents in an application for [MA] under Regulation (EC) No 726/2004 submitted to the [EMA], or in response to obligations laid down in that Regulation and Regulation (EC) No 1901/2006 to the extent that the infringement concerns a material particular'.

21 Article 16(1) of Regulation No 658/2007 states:

'Where, following the procedure provided for in Subsection 1, the Commission finds that the [MA] holder has committed, intentionally or negligently, an infringement as referred to in Article 1, it may adopt a decision imposing a fine not exceeding 5% of the holder's Community turnover in the preceding business year.'

The dispute in the main proceedings and the questions referred for a preliminary ruling

22 The AGCM, by decision of 27 February 2014 ('the AGCM's decision'), imposed two fines: one on Roche and its subsidiary Roche Italia, amounting to approximately EUR 90.6 million, and the other on Novartis and its subsidiary Novartis Italia, amounting to approximately EUR 92 million, on the ground that those undertakings had concluded an agreement contrary to Article 101 TFEU, designed to achieve an artificial differentiation between the medicinal products Avastin and Lucentis by manipulating the perception of the risks of using Avastin in the field of ophthalmology.

23 The two medicinal products at issue were developed by Genentech, a company established in the United States, which is active only in that country. Genentech entrusted the commercial exploitation of Avastin outside the United States to Roche, its parent company. Since the latter is not active in the field of ophthalmology, Genentech also entrusted the Novartis group with the commercial exploitation of Lucentis outside the United States, by way of a licensing agreement concluded in June 2003.

24 The MA for those medicinal products in the European Union is subject to the centralised procedure laid down in Regulation No 726/2004 on account of their biotechnological characteristics.

25 On 12 January 2005 the Commission granted an MA to Avastin for the treatment of certain tumorous diseases. On 26 September 2005 the Agenzia Italiana del farmaco (AIFA) (the Italian Medicines Agency) included Avastin in the list of medicinal products fully reimbursed by the national health system.

26 On 22 January 2007 the Commission also granted an MA to Lucentis for the treatment of eye diseases. On 31 May 2007, AIFA included Lucentis in the list of non-reimbursable medicinal products.

27 Prior to the placing on the market of Lucentis, some doctors had started prescribing Avastin to their patients with eye diseases. The prescription of Avastin in respect of indications not corresponding to those mentioned in the MA for that product ('off-label') for the treatment of such diseases began to spread worldwide. Given its lower unit price, the use of Avastin for those diseases continued after the placing on the market of Lucentis.

28 In accordance with Italian law, which allowed the off-label use of a medicinal product to be reimbursed in the absence of an authorised valid therapeutic alternative for the treatment of the disease in question, AIFA included, in May 2007, the use of Avastin in connection with the treatment of exudative macular diseases in the list of reimbursable medicinal products.

29 Following the inclusion, on 4 December 2008, of Lucentis and other medicinal products authorised for the treatment of the eye diseases in question in the list of reimbursable medicinal products in Italy, AIFA progressively excluded the reimbursement of off-label Avastin for those diseases.

30 By decision of 30 August 2012 the Commission, having obtained the favourable opinion of the EMA, amended the summary of Avastin's characteristics, in order to mention certain side effects associated with the use of that medicinal product for the treatment of eye diseases not covered by its MA.

31 Following the amendment of the summary of Avastin's characteristics, AIFA, on 18 October 2012, removed Avastin used for therapeutic indications not covered by its MA from the list of reimbursable medicinal products.

32 According to the AGCM's decision, the Roche group and the Novartis group entered into a market-sharing agreement that constitutes a restriction of competition by object. Paragraph 177 of that decision, inter alia, states that Avastin and Lucentis are equivalent in all respects for the treatment of eye diseases. According to that decision, the arrangement was intended to produce and disseminate opinions which could give rise to public concern regarding the safety of Avastin when used in ophthalmology and to downplay the value of scientific opinions to the contrary. That arrangement also related to the proceedings for amendment of the summary of Avastin's characteristics that were pending before the EMA and to the sending of a subsequent formal communication sent to healthcare professionals, both initiated by Roche.

33 According to the AGCM's decision, in particular paragraph 88 thereof, Avastin became the main competitor of Lucentis because of its widespread off-label use in Italy in the field of ophthalmology. The AGCM found, in paragraphs 82 to 88 of that decision, that the arrangement had given rise to a drop in Avastin sales and had caused a shift in demand toward Lucentis. Under paragraph 229 of the AGCM's decision, this had resulted in a cost increase for the national health service, assessed at approximately EUR 45 million in 2012 alone.

34 After the Tribunale amministrativo regionale per il Lazio (Regional Administrative Court, Lazio, Italy) dismissed the actions that they brought against that decision, Roche, Novartis and their Italian subsidiaries lodged an appeal before the Consiglio di Stato (Council of State, Italy).

35 The applicants in the main proceedings claim that, without the licensing agreement between Genentech and Novartis, it would not have been possible for the latter to enter the relevant market within a short space of time. In those circumstances, they argue that Roche and Novartis cannot be regarded as competitors, even potential ones. The applicants in the main proceedings consider that the parties to the licensing agreement could reasonably have provided in that agreement that Roche would not compete with Novartis, the licensee, on the relevant market. Such a restriction would, in their view, fall entirely outside the prohibition laid down in Article 101(1) TFEU.

36 The Consiglio di Stato (Council of State) decided to stay the proceedings and to refer the following questions to the Court for a preliminary ruling:

'(1) On a proper construction of Article 101 TFEU, can the parties to a licensing agreement be regarded as competitors if the licensee company operates on the relevant market concerned solely by virtue of that agreement? Do possible restrictions of competition between the licensor and the licensee in such a situation, although not expressly provided for in the licensing agreement, fall outside the scope of Article 101(1) TFEU or fall within the scope of the exception set out in Article 101(3) TFEU and, if so, within what limits?

(2) Does Article 101 TFEU allow the national competition authority to define the relevant market independently of the content of [MAs] for medicinal products granted by the competent pharmaceutical regulatory authorities ([AIFA and the EMA]) or, on the contrary, with respect to authorised medicinal products, must the relevant market for the purposes of Article 101 TFEU instead be held to be primarily shaped and established by the appropriate regulatory authority in a way that is binding even on the national competition authority?

(3) In the light of the provisions of Directive [2001/83], in particular Article 5 thereof, which relates to MAs for medicinal products, does Article 101 TFEU allow a medicinal product used off label and a medicinal product that has received an MA in respect of the same therapeutic indications [and is used in accordance with that MA] to be regarded as interchangeable and, thus, to be included in the same relevant market?

(4) Pursuant to Article 101 TFEU, for the purposes of defining the relevant market, is it important to establish, in addition to the substantive interchangeability of pharmaceutical products on the demand side, whether or not those products have been offered on the market in accordance with the regulatory framework for the marketing of medicinal products?

(5) In any event, can a concerted practice intended to emphasise that a medicinal product is less safe or less efficacious be regarded as a restriction of competition by object when the idea that that product is less efficacious or less safe, although not supported by reliable scientific evidence, cannot, in the light of the level of scientific knowledge available at the time of the events in question, be indisputably excluded either?'

The request to reopen the oral procedure

37 By letter dated 14 November 2017 Roche Italia requested that the oral procedure be reopened.

38 In support of its request, Roche Italia argues that the activity of launching a new medicinal product developed on the basis of Avastin was characterised as repackaging in points 68 and 82 of the Advocate General's Opinion, although that activity is a more complex task. It is also of the opinion that the judgment of 7 February 2013, *Slovenská sporiteľňa* (C-68/12, EU:C:2013:71), to which reference is made in points 89 and 166 of the Opinion, is irrelevant to the outcome of the present case.

39 It is a matter of settled case-law that the Court may, of its own motion, on a proposal from the Advocate General, or at the request of the parties, order the reopening of the oral procedure under Article 83 of its Rules of Procedure, if it considers that it lacks sufficient information or that the case must be decided on the basis of an argument which has not been debated between the parties (judgment of 15 September 2011, *Accor*, C-310/09, EU:C:2011:581, paragraph 19 and the case-law cited). By contrast, neither the Statute of the Court of Justice of the European Union nor its Rules of

Procedure make provision for the parties to submit observations in response to the Advocate General's Opinion (judgment of 16 December 2010, *Stichting Natuur en Milieu and Others*, C-266/09, EU:C:2010:779, paragraph 28 and the case-law cited).

40 The observations of Roche Italia are intended as a response to certain points of the Advocate General's Opinion. However, it follows from the case-law cited in the preceding paragraph that there is no provision in the texts governing procedure before the Court for the lodging of such observations.

41 In addition, after hearing the Advocate General, the Court finds that it has sufficient information to answer the questions submitted by the referring court and that all the arguments necessary for the determination of the matter at issue have been debated between the parties.

42 Consequently, the request to reopen the oral procedure must be rejected.

Admissibility of the request for a preliminary ruling

43 The AGCM, the Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds) and the Regione Emilia-Romagna (the Region of Emilia-Romagna, Italy) argue that the request for a preliminary ruling is inadmissible on the ground that it does not contain an adequate description of the facts of the case and of the parties' arguments.

44 In that regard, it must be borne in mind that, in the context of the cooperation between the Court and the national courts provided for in Article 267 TFEU, it is solely for the national court before which a dispute has been brought, and which must assume responsibility for the subsequent judicial decision, to determine in the light of the particular circumstances of the case both the need for a preliminary ruling in order to enable it to deliver judgment and the relevance of the questions which it submits to the Court. Consequently, where the questions submitted concern the interpretation of EU law, the Court is, in principle, bound to give a ruling (judgment of 6 September 2016, *Petruhhin*, C-182/15, EU:C:2016:630, paragraph 19 and the case-law cited).

45 It follows that questions on the interpretation of EU law referred by a national court in the factual and legislative context which that court is responsible for defining and the accuracy of which is not a matter for this Court to determine, enjoy a presumption of relevance. The Court may refuse to rule on a question referred by a national court only where it is quite obvious that the interpretation of EU law that is sought bears no relation to the actual facts of the main action or its purpose, where the problem is hypothetical, or where the Court does not have before it the factual or legal material necessary to give a useful answer to the questions submitted to it (judgment of 26 July 2017, *Persidera*, C-112/16, EU:C:2017:597, paragraph 24 and the case-law cited).

46 In the present case, however, the request for a preliminary ruling contains a description of the elements of fact and law behind the dispute that is sufficient to enable the Court to give a useful answer to the questions referred. Those questions, which relate to the interpretation of Article 101 TFEU, form part of a dispute concerning the validity of a decision through which the AGCM applied that provision. They thus bear a direct relation to the purpose of the main action and are not hypothetical. The AGCM and Aiudapds as well as the Region of Emilia-Romagna and all the parties that participated in the proceedings were able, moreover, to present their observations on the questions submitted by the referring court.

47 It follows that the questions referred for a preliminary ruling are admissible.

Consideration of the questions referred

The second to fourth questions

48 By its second to fourth questions, which it is appropriate to examine together, the referring court asks, in essence, whether Article 101 TFEU must be interpreted as meaning that, for the purposes of the application of that article, a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose MA does not cover such treatment but which is used for that purpose. If so, the referring court also asks whether the competition authority must take account of whether or not such off-label use complies with the EU rules governing pharmaceutical matters.

49 In order to answer those questions, it should be borne in mind that the sole purpose of the definition of the relevant market, in the context of the application of Article 101(1) TFEU, is to determine whether the agreement in question is capable of affecting trade between Member States and has the object or effect of preventing, restricting or distorting competition within the internal market (judgment of 11 July 2013, *Gosselin Group* v *Commission*, C-429/11 P, not published, EU:C:2013:463, paragraph 75 and the case-law cited).

50 The relevant product market comprises all those products and/or services which are regarded as interchangeable or substitutable by the consumer, by reason of their characteristics, their prices and their intended use (see judgment of 28 February 2013, *Ordem dos Técnicos Oficiais de Contas*, C-1/12, EU:C:2013:127, paragraph 77).

51 The concept of the relevant market implies that there can be effective competition between the products or services which form part of it and this presupposes that there is a sufficient degree of interchangeability between all the products or services forming part of the same market in so far as a specific use of such products or services is concerned (judgment of 13 February 1979, *Hoffmann-La Roche* v *Commission*, 85/76, EU:C:1979:36, paragraph 28). Interchangeability or substitutability is not assessed solely in relation to the objective characteristics of the products and services at issue. The competitive conditions and the structure of supply and demand on the market must also be taken into consideration (see, in respect of Article 102 TFEU, judgment of 9 November 1983, *Nederlandsche Banden-Industrie-Michelin* v *Commission*, 322/81, EU:C:1983:313, paragraph 37).

52 In that respect, it should be noted that the fact that pharmaceutical products are manufactured or sold illegally prevents them, in principle, from being regarded as substitutable or interchangeable products, both on the supply side, because of the legal, economic and technical risks, as well as the risks of reputational damage, to which they expose the manufacturers and distributors of those products, and on the demand side, in particular due to the risk to public health that they cause among healthcare professionals and patients.

53 Under Article 6 of Directive 2001/83, no medicinal product may be placed on the market of a Member State unless an MA has been issued by the competent authorities of that Member State in accordance with that directive or an authorisation has been granted in accordance with Regulation No 726/2004.

54 In the present case, however, it is not disputed that during the alleged infringement period Avastin was covered by an MA validly issued by the Commission pursuant to that regulation for the treatment of tumorous diseases.

55 The dispute in the main proceedings concerns the use of Avastin for the treatment of eye diseases which were not covered by that MA. The referring court thus asks, in essence, whether the AGCM could include that off-label use of Avastin in the relevant market, even in the event that it failed to comply with the requirements laid down by the EU rules on pharmaceutical products. Indeed, Roche

argues on that point that a significant proportion, the majority even, of the Avastin intended for off-label use in Italy was serially repackaged without manufacturing authorisation and was sold to healthcare providers in advance, before the submission of individual prescriptions.

56 In that respect, it should be noted that Directive 2001/83 does not prohibit the use of medicinal products for therapeutic indications not covered by their MA. Article 5(1) of Directive 2001/83 in fact provides that a Member State may, in order to fulfil special needs, exclude from the provisions of that directive medicinal products supplied in response to a *bona fide* unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional for use by an individual patient under his direct personal responsibility.

57 On that point, the Court has held that it is apparent from all the conditions set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the objective of seeking to safeguard public health, that the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market (judgments of 29 March 2012, *Commission* v *Poland*, C-185/10, EU:C:2012:181, paragraph 36, and of 16 July 2015, *Abcur*, C-544/13 and C-545/13, EU:C:2015:481, paragraph 56).

58 In addition, the EU rules on pharmaceutical matters govern the conditions under which a medicinal product such as Avastin may be repackaged so as to allow its intravitreal injection. Thus, according to Article 40 of Directive 2001/83, the manufacture of a medicinal product is subject to authorisation, except for repackaging carried out for retail supply by healthcare professionals (judgment of 28 June 2012, *Caronna*, C-7/11, EU:C:2012:396, paragraph 35). The repackaging of Avastin with a view to its use in ophthalmology therefore requires an authorisation, as a rule, unless it is carried out solely for the purposes of retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States (judgment of 11 April 2013, *Novartis Pharma*, C-535/11, EU:C:2013:226, paragraph 52).

59 It follows that the EU rules on pharmaceutical products prohibit neither the off-label prescription of a medicinal product nor its repackaging for such use but do require that they comply with the conditions laid down in those rules.

60 Furthermore, as the Advocate General pointed out in point 88 of his Opinion, it is not for the national competition authorities to verify compliance with EU law of the conditions under which a medicinal product such as Avastin is prescribed by doctors, on the demand side, and repackaged, on the supply side, with a view to its off-label use. Such verification can be carried out comprehensively only by the authorities with jurisdiction to ensure compliance with the rules governing pharmaceutical matters, or by the national courts.

61 Therefore, in order to assess the extent to which a pharmaceutical product whose MA does not cover the treatment of certain diseases is substitutable or interchangeable with another pharmaceutical product that is authorised for the treatment of those diseases, and whether those products therefore fall within the same relevant market as defined in paragraphs 50 and 51 above, the national competition authority must, in so far as conformity of the product at issue with the applicable provisions governing the production or the marketing of the product has been examined by the competent authorities or courts, take account of the outcome of that examination by assessing any effects it may have on the structure of supply and demand.

62 With regard to the dispute in the main proceedings, there is nothing in the case file to suggest that, at the time the AGCM applied Article 101 TFEU, any unlawfulness of the conditions under which Avastin was repackaged and prescribed with a view to its off-label use, as alleged by Roche, had been established by either the authorities jurisdiction to ensure compliance with the rules governing pharmaceutical matters or by the national courts.

63 On the contrary, without prejudice to the verifications which are a matter for the referring court to determine, as the case may be, it is apparent, in particular from paragraphs 70 and 208 of the AGCM's decision, that, at the time the decision was adopted, the EMA and the Commission did not grant Roche's request to include in the list of 'adverse reactions' set out in the summary of Avastin's characteristics certain side effects resulting from the intravitreal use of that product, and that they took the view that those effects warranted only a mention in the 'Special warnings and precautions for use'.

64 In those circumstances, the state of uncertainty surrounding the lawfulness of the repackaging and the prescription of Avastin for the treatment of eye diseases did not preclude the AGCM, for the purposes of the application of Article 101(1) TFEU, from finding that that product belonged to the same market as another medicinal product whose MA covers specifically those therapeutic indications.

65 It should also be stressed in this regard that, given the specific features of competition in the pharmaceutical sector, the relevant market for the purposes of the application of Article 101(1) TFEU is, in principle, capable of comprising medicinal products that may be used for the same therapeutic indications, since the prescribing doctors are primarily guided by considerations of therapeutic appropriateness and the efficacy of medicines.

66 However, it is not disputed between the parties to the main proceedings that during the infringement period referred to in the AGCM's decision Avastin was frequently prescribed for the treatment of eye diseases, despite the fact that its MA did not cover those indications. Consequently, this circumstance reveals the existence of a specific relationship of substitutability between that medicinal product and the products authorised for those eye diseases, which include Lucentis. It is all the more true that it was possible to assess accurately the demand for that product for the treatment of eye diseases not covered by its MA since Avastin was subject to prescription.

67 In view of the above, the answer to the second to fourth questions is that Article 101 TFEU must be interpreted as meaning that, for the purposes of the application of that article, a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose MA does not cover that treatment but which is used for that purpose and is thus actually substitutable with the former. In order to determine whether such a relationship of substitutability exists, the competition authority must, in so far as conformity of the product at issue with the applicable provisions governing the manufacture or the marketing of that product has been examined by the competent authorities or courts, take account of the outcome of that examination by assessing any effects it may have on the structure of supply and demand.

The first part of the first question

68 By the first part of its first question the referring court asks whether, in essence, Article 101(1) TFEU must be interpreted as meaning that any restrictions of competition agreed between the parties to a licensing agreement fall outside the scope of application of the first paragraph of that article even though the licensing agreement does not envisage any such restrictions on the ground that they are ancillary to that agreement.

69 In that regard, it is apparent from the case-law of the Court that if a given operation or activity is not covered by the prohibition laid down in Article 101(1) TFEU, owing to its neutrality or positive effects in terms of competition, a restriction of the commercial autonomy of one or more of the participants in that operation or activity is not covered by that prohibition either if that restriction is objectively necessary to the implementation of that operation or that activity and is proportionate to the objectives of one or the other (see judgment of 11 September 2014, *MasterCard and Others* v *Commission*, C-382/12 P, EU:C:2014:2201, paragraph 89 and the case-law cited).

70 Where it is not possible to dissociate such a restriction from the main operation or activity without jeopardising its existence and aims, it is necessary to examine the compatibility of that restriction with Article 101 TFEU in conjunction with the compatibility of the main operation or activity to which it is ancillary, even though, taken in isolation, such a restriction may appear on the face of it to be covered by the prohibition rule in Article 101(1) TFEU (judgment of 11 September 2014, *MasterCard and Others* v *Commission*, C-382/12 P, EU:C:2014:2201, paragraph 90).

71 Where it is a matter of determining whether a restriction can escape the prohibition laid down in Article 101(1) TFEU because it is ancillary to a main operation that is not anticompetitive in nature, it is necessary to inquire whether that operation would be impossible to carry out in the absence of the restriction in question. The fact that that operation is simply more difficult to implement or even less profitable without the restriction concerned cannot be deemed to give that restriction the objective necessity required in order for it to be classified as ancillary. Such an interpretation would effectively extend that concept to restrictions which are not strictly indispensable to the implementation of the main operation. Such an outcome would undermine the effectiveness of the prohibition laid down in Article 101(1) TFEU (judgment of 11 September 2014, *MasterCard and Others* v *Commission*, C-382/12 P, EU:C:2014:2201, paragraph 91).

72 In the present case, it should be noted that the conduct described in the AGCM's decision, which concerns the dissemination of allegedly misleading information relating to adverse reactions to Avastin where that product is administered for the treatment of eye diseases, was not designed to restrict the commercial autonomy of the parties to the licensing agreement regarding Lucentis but rather the conduct of third parties, in particular healthcare professionals, with a view to preventing the use of Avastin for that type of treatment from interfering with the use of Lucentis for that same purpose.

73 Furthermore, while, admittedly, the file submitted to the Court contains no information that is capable of casting doubt on the favourable, or at least neutral, nature, in terms of competition, of the licence agreement concluded between Genentech and Novartis, it cannot be held that conduct such as that described in the preceding paragraph was objectively necessary for the implementation of the agreement. Indeed, that conduct was agreed upon several years after the agreement was concluded, and not in the agreement itself or upon its conclusion, with a view to eliminating the substitutability between the use of Avastin and that of Lucentis for the purpose of treating eye diseases, arising in particular from the prescribing practices of doctors.

74 The fact that the conduct penalised in the AGCM's decision was designed to reduce the use of Avastin and to increase the use of Lucentis so as to render more profitable the exploitation by Novartis of the technology rights over Lucentis granted to it by Genentech cannot mean, in the light of the case law referred to in paragraph 71 above, that that conduct is to be regarded as objectively necessary for the implementation of the licensing agreement at issue.

75 In view of the foregoing, the answer to the first part of the first question is that Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between the parties to a licensing agreement regarding the exploitation of a medicinal product which, in order to reduce competitive pressure on the use of that product for the treatment of given diseases, is designed to restrict the

conduct of third parties promoting the use of another medicinal product for the treatment of those diseases, does not fall outside the application of that provision on the ground that the arrangement is ancillary to that agreement.

The fifth question

76 It is clear from the explanations provided by the referring court and the observations submitted to the Court that the finding of infringement of Article 101 TFEU by the undertakings at issue in the main proceedings concerns only the dissemination of information relating to adverse reactions resulting from the off-label use of Avastin.

77 Although the fifth question also refers to information concerning the efficacy of a medicinal product, it must be considered that, by this question, the referring court is asking, in essence, whether Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between two undertakings marketing two competing products, which concerns the dissemination, in a context of scientific uncertainty on the matter, of information relating to adverse reactions resulting from the use of one of those medicinal products for indications not covered by its MA, with a view to reducing the competitive pressure resulting from that use on another medicinal product covered by an MA covering those indications, constitutes a restriction of competition 'by object' for the purposes of that provision.

78 In that regard, it is important to recall that the concept of restriction of competition 'by object' must be interpreted strictly and can be applied only to certain types of coordination between undertakings which reveal a degree of harm to competition that is sufficient for it to be held that there is no need to examine their effects. Indeed, certain forms of coordination between undertakings can be regarded, by their very nature, as being harmful to the proper functioning of normal competition (see, inter alia, judgments of 20 November 2008, *Beef Industry Development Society and Barry Brothers*, C-209/07, EU:C:2008:643, paragraph 17, and of 27 April 2017, *FSL and Others* v *Commission*, C-469/15 P, EU:C:2017:308, paragraph 103).

79 In order to determine whether an arrangement can be considered to be a restriction of competition by object, regard must be had to the content of its provisions, its objectives and the economic and legal context of which it forms a part (see, to that effect, judgments of 8 November 1983, *IAZ International Belgium and Others* v *Commission*, 96/82 to 102/82, 104/82, 105/82, 108/82 and 110/82, EU:C:1983:310, paragraph 25, and of 11 September 2014, *CB* v *Commission*, C-67/13 P, EU:C:2014:2204, paragraph 53).

80 When determining that context, it is necessary to take into account the nature of the goods or services affected, as well as the real conditions of the functioning and the structure of the market or markets in question (judgment of 23 November 2006, *Asnef-Equifax and Administración del Estado*, C-238/05, EU:C:2006:734, paragraph 49 and the case-law cited). Where the question arises as to whether there is a cartel agreement in the pharmaceuticals sector, account must be taken of the impact of EU rules on pharmaceutical products (see, by analogy, judgment of 16 September 2008, *Lélos kai Sia and Others*, C-468/06 to C-478/06, EU:C:2008:504, paragraph 58).

81 Those rules require that a medicinal product such as Avastin must be subject to a pharmacovigilance system under the control of the EMA in coordination with the competent national agencies for pharmaceutical matters. Under the second paragraph of Article 101(1) of amended Directive 2001/83, '[that system] shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the [MA] as well as from use outside the terms of the [MA], and to adverse reactions associated with occupational exposure'.

82 With regard to medicinal products authorised through the centralised procedure, Article 16(2) of Regulation No 726/2004 imposes on the holder of the MA an obligation to forthwith supply to the EMA, to the Commission and to the Member States any new information which might entail the variation of the information required for issuance of the MA, including the information set out in the summary of the product characteristics.

83 Those obligations were strengthened as from 2 July 2012, the date on which the amendment to Article 16(2) of Regulation No 726/2004 introduced by Regulation No 1235/2010 became applicable. Article 16(2) of amended Regulation No 726/2004 thus provides that the MA holder 'shall forthwith inform the [EMA] and the Commission … with any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned', with that information comprising 'both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the [MA], as well as data on the use of the medicinal product where such use is outside the terms of the [MA].'

84 In addition, pursuant to Article 17 of Regulation No 726/2004, the holder of the MA is responsible for the accuracy of the documents and the data provided.

85 Moreover, the conditions for dissemination of information on medicinal products to healthcare professionals and the general public are governed, in particular, by Article 106a of amended Directive 2001/83, which applies to the holder of an MA granted in accordance with the centralised procedure under Article 22 of amended Regulation No 726/2004. Under Article 106a of amended Directive 2001/83, the MA holder must ensure that 'that information to the public is presented objectively and is not misleading'. Article 24(5) of Regulation No 726/2004, also applicable to the facts at issue in the main proceedings and repealed with effect from 2 July 2012 by Regulation No 1235/2010, was worded in comparable terms to Article 106a of amended Directive 2001/83.

86 In order to ensure the efficacy of the implementation of the rules governing pharmaceutical matters, they are combined with penalties. With regard to the centralised procedure, Article 84 of Regulation No 726/2004 provides that the Member States are to determine the applicable penalties, which must be 'effective, proportionate and dissuasive'. That article also provides that the Commission may impose penalties if the MA holder fails to observe the conditions laid down in the MA.

87 The procedure and financial penalties were subsequently specified in Regulation No 658/2007, which stipulates in Article 16(1) thereof that the Commission may impose penalties in the form of fines amounting to up to 5% of the MA holder's annual turnover within the European Union. The list of infringements set out in Article 1(1) of the regulation, in respect of which the Commission may impose penalties in cases where the infringement concerned may have significant public health implications in the European Union, where it has an EU dimension because it takes place or has its effects in more than one Member State, or where EU interests are involved, includes infringement of the obligation to provide complete and accurate particulars and documents in an application for an MA under Regulation No 726/2004 or any other documents and data to be submitted to the EMA in response to the obligations laid down in the regulation.

88 Moreover, in accordance with Article 28(4) of amended Regulation No 726/2004, the EMA and the Commission have exclusive jurisdiction to examine applications for variation of an MA in connection with amendments made to the summary of product characteristics owing to new pharmacovigilance information and, as the case may be, to adopt a decision to vary, suspend or revoke the MA concerned.

89 With regard to the facts at issue in the main proceedings, which are a matter for the referring court alone, as is apparent from paragraphs 177, 189, 193 to 202 and 209 of the AGCM's decision, the AGCM found that by adopting a common strategy to counteract the competitive pressure exerted on the sale of Lucentis by the use of Avastin for the treatment of eye diseases not covered by its MA, the

undertakings concerned infringed Article 101 TFEU. According to that decision, the purpose of the arrangement put in place between Roche and Novartis was to create an artificial differentiation between those two medicinal products by manipulating the perception of the risks associated with the use of Avastin for the treatment of those diseases through the production and dissemination of opinions which, based on an 'alarmist' interpretation of available data, could give rise to public concern regarding the safety of certain uses of Avastin and influence the therapeutic choices of doctors, and by downplaying any scientific knowledge to the contrary.

90 Under paragraph 177 of the AGCM's decision, this arrangement was also intended to disclose to the EMA information that could exaggerate the perception of the risks associated with that use in order to obtain the amendment of the summary of Avastin's characteristics and to be granted leave to send healthcare professionals a letter drawing their attention to such adverse reactions. According to paragraphs 208, 209 and 215 of the AGCM's decision, this artificial exaggeration of the risks associated with the off-label use of Avastin is substantiated, inter alia, by the fact mentioned in paragraph 63 above that the EMA and the Commission did not grant Roche's request to include in the list of 'adverse reactions' set out in the summary of Avastin's characteristics certain side effects resulting from the intravitreal use of Avastin, and that they took the view that those effects warranted only a mention in the 'Special warnings and precautions for use'.

91 In that regard, it should be noted, in the first place, before even examining the relevance for the purpose of establishing a restriction of competition by object under Article 101(1) TFEU of the misleading nature of the information supplied to the EMA and the general public, that the requirements for pharmacovigilance that might call for steps to be taken such as the dissemination to healthcare professionals and the general public of information relating to the risks associated with the off-label use of a medicinal product, as well as the initiation of a procedure before the EMA with a view to including such information in the summary of characteristics of the product, rest, as is apparent from the provisions referred to in paragraph 82 and 87 above, solely with the holder of the MA for that medicinal product and not with another undertaking marketing a competing medicinal product covered by a separate MA. Accordingly, the fact that two undertakings marketing competing pharmaceutical products collude with each other with a view to disseminating information specifically relating to the product marketed by only one of them might constitute evidence that the dissemination of information pursues objectives unrelated to pharmacovigilance.

92 In the second place, with regard to the misleading nature of the information at issue, it must be held that the information whose notification to the EMA and the general public, according to the AGCM's decision, was the subject of a cartel agreement between Roche and Novartis, are, failing compliance with the requirements of completeness and accuracy laid down in Article 1(1) of Regulation No 658/2007, to be regarded as misleading if the purpose of that information, which is a matter for the referring court to determine, was (i) to confuse the EMA and the Commission and have the adverse reactions mentioned in the summary of product characteristics so as to enable the MA holder to launch a communication campaign aimed at healthcare professionals, patients and other persons concerned with a view to exaggerating that perception artificially, and (ii) to emphasise, in a context of scientific uncertainty, the public perception of the risks associated with the off-label use of Avastin, given, inter alia, the fact that the EMA and the Commission did not amend the summary of characteristics of that product in respect of its 'adverse reactions' but merely issued 'Special warnings and precautions for use'.

93 However, in such a case, given the characteristics of the medicinal products market, it is likely that the dissemination of such information will encourage doctors to refrain from prescribing that product, thus resulting in the expected reduction in demand for that type of use. The provision of misleading information to the EMA, healthcare professionals and the general public, as is apparent from paragraphs 84 to 87 above, also constitutes an infringement of the EU rules governing pharmaceutical matters giving rise to penalties.

94 In those circumstances, an arrangement that pursues the objectives described in paragraph 92 above must be regarded as being sufficiently harmful to competition to render an examination of its effects superfluous.

95 In the light of the foregoing, the answer to the fifth question is that Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between two undertakings marketing two competing products, which concerns the dissemination, in a context of scientific uncertainty, to the EMA, healthcare professionals and the general public of misleading information relating to adverse reactions resulting from the use of one of those products for the treatment of diseases not covered by the MA for that product, with a view to reducing the competitive pressure resulting from such use on the use of the other medicinal product, constitutes a restriction of competition 'by object' for the purposes of that provision.

The second part of the first question

96 By the second part of its first question, the referring court also asks whether Article 101 TFEU must be interpreted as meaning that an arrangement such as that described in the previous paragraph can be exempt under Article 101(3) TFEU.

97 The applicability of the exemption provided for in Article 101(3) TFEU is subject to the four cumulative requirements laid down in that provision. Those requirements are, first, that the arrangement concerned must contribute to improving the production or distribution of the goods or services in question, or to promoting technical or economic progress; secondly, that consumers must be allowed a fair share of the resulting benefit; thirdly, that it must not impose on the participating undertakings restrictions that are not indispensable; and, fourthly, that it must not afford them the possibility of eliminating competition in respect of a substantial part of the products or services in question.

98 In the present case, however, suffice it to note that the dissemination of misleading information in respect of a medicinal product cannot be regarded as 'indispensable' within the meaning of the third requirement for the purpose of being exempt under Article 101(3) TFEU.

99 By referring several times to a licensing agreement and to the existence of a relationship of competition between the parties to that agreement, the referring court seems to have intended, by its first question, to refer to the requirements laid down in Commission Regulation (EC) No 772/2004 of 27 April 2004 on the application of Article 81(3) of the Treaty to categories of technology transfer agreements (OJ 2004 L 123, p. 11).

100 However, it is important to note that, in the light of the considerations set out in paragraphs 97 and 98 above and pursuant to Article 101(3) TFEU, an arrangement such as that at issue in the main proceedings cannot, in any event, be exempt under Article 2 of the regulation.

101 Therefore, the answer to the second part of the first question is that Article 101 TFEU must be interpreted as meaning that an arrangement such as that described in paragraph 9 above cannot be exempt under Article 101(3) TFEU.

Costs

102 Since these proceedings are, for the parties to the main proceedings, a step in the action pending before the national court, the decision on costs is a matter for that court. Costs incurred in submitting observations to the Court, other than the costs of those parties, are not recoverable.

On those grounds, the Court (Grand Chamber) hereby rules:

1. **Article 101 TFEU must be interpreted as meaning that, for the purposes of the application of that article, a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose marketing authorisation does not cover that treatment but which is used for that purpose and is thus actually substitutable with the former. In order to determine whether such a relationship of substitutability exists, the competition authority must, in so far as conformity of the product at issue with the applicable provisions governing the manufacture or the marketing of that product has been examined by the competent authorities or courts, take account of the outcome of that examination by assessing any effects it may have on the structure of supply and demand.**

2. **Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between the parties to a licensing agreement regarding the exploitation of a medicinal product which, in order to reduce competitive pressure on the use of that product for the treatment of given diseases, is designed to restrict the conduct of third parties promoting the use of another medicinal product for the treatment of those diseases, does not fall outside the application of that provision on the ground that the arrangement is ancillary to that agreement.**

3. **Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between two undertakings marketing two competing products, which concerns the dissemination, in a context of scientific uncertainty, to the European Medicines Agency, healthcare professionals and the general public of misleading information relating to adverse reactions resulting from the use of one of those medicinal products for the treatment of diseases not covered by the marketing authorisation of that product, with a view to reducing the competitive pressure resulting from such use on the use of the other product, constitutes a restriction of competition 'by object' for the purposes of that provision.**

4. **Article 101 TFEU must be interpreted as meaning that such an arrangement cannot be exempt under Article 101(3) TFEU.**

[Signatures]