Reports of Cases

JUDGMENT OF THE GENERAL COURT (Sixth Chamber)

22 January 2015 *

(Medicinal products for human use — Orphan medicinal products — Application for marketing authorisation for the generic version of the orphan medicinal product imatinib — EMA decision refusing to validate the application for marketing authorisation — Market exclusivity)

In Case T-140/12,

Teva Pharma BV, established in Utrecht (Netherlands),

Teva Pharmaceuticals Europe BV, established in Utrecht,

represented by D. Anderson, QC, K. Bacon, Barrister, G. Morgan and C. Drew, Solicitors,

applicants,

v

European Medicines Agency (EMA), represented by T. Jabłoński, M. Tovar Gomis and N. Rampal Olmedo, acting as Agents,

defendant,

supported by

European Commission, represented by E. White, P. Mihaylova and M. Šimerdová, acting as Agents,

intervener,

APPLICATION for annulment of the EMA's decision of 24 January 2012 refusing to validate the applicants' application for marketing authorisation for imatinib Ratiopharm, a generic version of the orphan medicinal product imatinib, in so far as concerns therapeutic indications for the treatment of chronic myeloid leukaemia,

THE GENERAL COURT (Sixth Chamber),

composed of S. Frimodt Nielsen (Rapporteur), President, F. Dehousse and A.M. Collins, Judges,

Registrar: S. Spyropoulos, Administrator,

having regard to the written procedure and further to the hearing on 11 September 2014,

gives the following

* Language of the case: English.

Judgment

Legal context

Regulation (EC) No 141/2000

1 In order to promote the development of effective treatment for patients suffering from rare diseases in the European Union, the European Parliament and the Council of the European Union adopted Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products (OJ 2000 L 18, p. 1). That regulation, which entered into force on 22 January 2000, introduces a system of initiatives to encourage pharmaceutical companies to invest in the research, development and marketing of medicinal products intended for the diagnosis, prevention or treatment of rare diseases, which are referred to as 'orphan medicinal products'.

2 Regulation No 141/2000 lays down specific, separate procedures for the designation of medicinal products as orphan medicinal products and for the marketing authorisation of such products.

3 As regards the designation of medicinal products as orphan medicinal products, Article 3 of Regulation No 141/2000 sets out the criteria for designation, while Article 5 of the regulation lays down the procedure to be followed for the designation of such products and for their removal from the Community Register of Orphan Medicinal Products.

4 Article 3(1) of Regulation No 141/2000 is worded as follows:

'A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made,

or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.'

5 The procedure for designation, as laid down in Article 5 of Regulation No 141/2000, is as follows:

'1. In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the [European Medicines] Agency at any stage of the development of the medicinal product before the application for marketing authorisation is made.

…

4. The Agency shall verify the validity of the application and prepare a summary report to the Committee [for Orphan Medicinal Products]. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application.

5. The Agency shall ensure that an opinion is given by the Committee within 90 days of the receipt of a valid application.

…

8. The Agency shall forthwith forward the final opinion of the Committee to the Commission, which shall adopt a decision within 30 days of receipt of the opinion. … The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.

9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.

…

12. A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products:

(a) at the request of the sponsor;

(b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned;

(c) at the end of the period of market exclusivity as laid down in Article 8.'

6 As regards the marketing authorisation of designated orphan medicinal products, Article 7 of Regulation No 141/2000 lays down the procedure to be followed and Article 8 thereof sets out the conditions attaching to the market exclusivity conferred by the marketing authorisation.

7 Article 7 of Regulation No 141/2000 states as follows:

'1. The person responsible for placing on the market an orphan medicinal product may request that authorisation to place the medicinal product on the market be granted by the Community in accordance with the provisions of Regulation … No 2309/93 …

…

3. The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. This is without prejudice to the possibility of applying for a separate marketing authorisation for other indications outside the scope of this Regulation.'

8 Article 8 of Regulation No 141/2000 provides that orphan medicinal products for which a marketing authorisation has been granted are to benefit from market exclusivity:

'1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, and without prejudice to intellectual property law or any other provision of Community law, the

Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

…

3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of [European Union] law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

4. The Commission shall adopt definitions of "similar medicinal product" and "clinical superiority" in the form of an implementing Regulation in accordance with the procedure laid down in Article 72 of Regulation (EEC) No 2309/93.

…'

Regulation (EC) No 847/2000

9 Article 3(2) of Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ 2000 L 103, p. 5) provides as follows:

'For the purposes of the implementation of Article 3 of Regulation … No 141/2000 on orphan medicinal products, the following definition shall apply:

— "significant benefit" means a clinically relevant advantage or a major contribution to patient care.'

Background to the dispute

10 On 14 February 2001, the Commission of the European Communities adopted a decision designating the medicinal product imatinib melysate ('imatinib') as an orphan medicinal product for the treatment of chronic myeloid leukaemia ('CML') and entering that product in the Community Register of Orphan Medicinal Products in accordance with Article 5(9) of Regulation No 141/2000.

11 On 7 November 2001, the Commission adopted a decision authorising the marketing of the medicinal product imatinib under the commercial name Glivec for the following therapeutic indications: the treatment of adult patients with CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. Other therapeutic indications relating to the treatment of Ph+ acute lymphoblastic leukaemia, myelodysplastic syndromes or myeloproliferative diseases, advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia, gastrointestinal stromal tumours and

Darier-Ferrand dermatofibrosarcoma have been the subject of successive Commission decisions concerning, respectively, their entry in the Community Register of Orphan Medicinal Products and the variation of the marketing authorisation for that medicinal product in respect of those therapeutic indications.

12 Pursuant to Article 8 of Regulation No 141/2000, the period of market exclusivity enjoyed by the medicinal product imatinib, marketed under the commercial name Glivec, in so far as concerns the CML therapeutic indications — the original marketing authorisation for which took effect on 12 November 2001 — expired on 12 November 2011.

13 On 2 February 2006, the pharmaceutical company which developed imatinib and marketed that medicinal product under the commercial name Glivec submitted an application to the European Medicines Agency ('EMA') for the designation of a new product which it had developed for the treatment of CML as an orphan medicinal product, namely the medicinal product nilotinib.

14 Following the favourable opinion of the EMA's Committee for Orphan Medicinal Products ('the COMP') of 5 April 2006, the Commission concluded that nilotinib satisfied the designation criteria laid down in Article 3(1) of Regulation No 141/2000 and, on 22 May 2006, adopted a decision designating nilotinib as an orphan medicinal product for the treatment of CML and providing for its entry in the Community Register of Orphan Medicinal Products.

15 In the course of the marketing authorisation procedure for the medicinal product nilotinib and following an opinion of the EMA's Committee for Medicinal Products for Human Use concluding that imatinib and nilotinib were to regarded as similar medicinal products, the holder of the authorisation for the marketing of imatinib under the commercial name Glivec notified the EMA that it consented to authorisation being granted for the marketing of the similar medicinal product nilotinib under the commercial name Tasigna for the same therapeutic indications, in accordance with Article 8(3)(a) of Regulation No 141/2000.

16 On the basis of a summary report of the COMP of 8 November 2007, that committee gave an opinion on 14 November 2007, for the purpose of Article 5(12) of Regulation No 141/2000, recommending that nilotinib should not be removed from the Community Register of Orphan Medicinal Products as it had been established that nilotinib would be of significant benefit to patients with CML, even though a satisfactory treatment already existed for CML.

17 On 19 November 2007, the Commission adopted a decision authorising the marketing of the medicinal product nilotinib under the commercial name Tasigna for the following therapeutic indications: the treatment of adult patients with CML in chronic phase and accelerated phase, with resistance or intolerance to prior treatment involving imatinib. That decision was included in the summary of decisions on marketing authorisations in respect of medicinal products from 1 November 2007 to 30 November 2007, published in the *Official Journal of the European Union* on 28 December 2007 (OJ 2007 C 316, p. 48).

18 On 20 December 2010, the Commission adopted a decision varying the authorisation for the marketing of the medicinal product nilotinib under the commercial name Tasigna with a view to extending its therapeutic indications to include the treatment of adult patients with newly diagnosed CML in chronic phase. That decision was included in the summary of European Union decisions on marketing authorisations in respect of medicinal products from 1 November 2010 to 31 December 2010, published in the Official Journal on 25 February 2011 (OJ 2011 C 61, p. 1).

19 On 5 January 2012, Teva Pharmaceuticals Europe BV ('Teva Europe') submitted an application on behalf of a company within the same group, namely Teva Pharma BV ('Teva'), for authorisation to place on the market a generic version of medicinal product marketed under the commercial name Glivec, namely imatinib Ratiopharm, for therapeutic indications covering, first, the treatment of adult

patients with newly diagnosed CML in chronic phase for whom bone marrow transplantation cannot be considered as a first line of treatment and adult patients with CML in chronic phase after failure of interferon-alpha therapy or in accelerated phase and, second, the treatment of the non-CML cancer indications for which the original orphan medicinal product had also been authorised.

20 By letter of 24 January 2012 to Teva Europe ('the contested decision'), the EMA refused to validate the application of 5 January 2012 in so far as it covered CML the therapeutic indications for which the orphan medicinal product marketed under the commercial name Tasigna enjoyed marketing authorisation, as well as other non-CML orphan therapeutic indications for which the medicinal product marketed under the commercial name Glivec enjoyed marketing authorisation, on the ground that those indications were still subject to market exclusivity protection under Article 8(1) of Regulation No 141/2000. The EMA also stated that it was in a position to accept applications for marketing authorisation in respect of generic versions of the medicinal product Glivec for therapeutic indications that were not covered by market exclusivity under Article 8(1) of Regulation No 141/2000.

Procedure and forms of order sought by the parties

21 The applicants, Teva and Teva Europe, brought the present action by application lodged at the Registry of the General Court on 28 March 2012.

22 By document lodged at the Court Registry on 24 July 2012, the Commission sought leave to intervene in the present proceedings in support of the EMA. By order of 6 September 2012, the President of the First Chamber of the General Court granted the Commission leave to intervene. The intervener lodged its statement in intervention and the other parties lodged their observations on the statement within the periods prescribed.

23 Following changes in the composition of the Chambers of the General Court, the present case was assigned to the Sixth Chamber.

24 Upon hearing the Report of the Judge-Rapporteur, the General Court (Sixth Chamber) decided to open the oral procedure and, by way of measures of organisation of procedure provided for in Article 64 of the Rules of Procedure of the General Court, put written questions to the defendant, which answered them within the period prescribed.

25 At the hearing on 11 September 2014, the parties presented oral argument and answered the questions put to them by the Court.

26 The applicants claim that the Court should:

— annul the contested decision;

— order the EMA to pay the costs.

27 The EMA, supported by the Commission, contends that the Court should:

— dismiss the action as unfounded;

— order the applicants to pay the costs.

Law

28 The applicants put forward two pleas in law in support of their action. The first plea alleges infringement of Article 8(1) and (3) of Regulation No 141/2000 in so far as the EMA misinterpreted those provisions by refusing to validate the application for marketing authorisation in respect of the medicinal product imatinib Ratiopharm. The second ground, raised at the stage of the reply, alleges infringement of Article 3(1)(b) of Regulation No 141/2000, on the basis that, as nilotinib did not satisfy the conditions laid down in that provision when its marketing authorisation was granted, the EMA was not entitled to rely on its status as an orphan medicinal product or its market exclusivity when it rejected the application for marketing authorisations submitted by the applicants.

29 Since the market exclusivity granted to an orphan medicinal product under Article 8(1) of Regulation No 141/2000 is based on the premiss that the medicinal product in question enjoys the status of orphan medicinal product in accordance with Article 3(1) of that regulation, it is appropriate to analyse the applicants' second plea first.

The plea alleging infringement of Article 3(1)(b) of Regulation No 141/2000

30 In the reply, the applicants put forward an additional ground for annulment of the contested decision, based on infringement of Article 3(1)(b) of Regulation No 141/2000.

31 The applicants maintain that it is apparent from the COMP's summary report of 8 November 2007 and its opinion of 14 November 2007 that that committee did not conclude that the medicinal product nilotinib represented a significant benefit to patients suffering from CML by comparison with all other existing forms of treatment, in particular treatment based on the medicinal product dasatinib, and simply stated that nilotinib 'may' be of 'potential' significant benefit to patients suffering from CML. Article 3(1)(b) of Regulation No 141/2000 provides that, in order to be designated as an orphan medicinal product, such a product must be of significant benefit by comparison with existing treatments. It follows that that committee was incorrect to conclude in its opinion of 14 November 2007 that the medicinal product nilotinib was not to be removed from the Community Register of Orphan Medicinal Products.

32 Invoking Article 277 TFEU, the applicants contend that the COMP's summary report of 8 November 2007 and its opinion of 14 November 2007 are inapplicable and that, as a result, the continued inclusion of the medicinal product nilotinib in the Community Register of Orphan Medicinal Products and the authorisation enabling that product to enjoy market exclusivity pursuant to Article 8(1) of Regulation No 141/2000 are also invalid.

33 The EMA and the Commission contest those arguments, maintaining, first of all, that the additional ground for annulment, put forward by the applicants at the stage of the reply, is out of time and, accordingly, inadmissible in accordance with Article 48(2) of the Rules of Procedure.

34 The applicants argue that their additional ground for annulment is admissible because it was raised in response to material which came to light in the course of the present procedure. They became aware of the fact that, in its summary report of 8 November 2007 and its opinion of 14 November 2007, the COMP had not concluded that the medicinal product nilotinib represented a significant benefit only when those two documents, which had not been made available to the public previously, were produced by the EMA in the defence.

35 First, as regards the admissibility of the plea put forward by the applicants for the first time in the reply, it should be borne in mind that, under Article 48(2) of the Rules of Procedure, no new plea in law may be introduced in the course of proceedings unless it is based on matters of law or of fact which come to light in the course of the procedure.

36 In that connection, according to case-law, the fact that a party became aware of a factual matter during the course of the procedure before the General Court does not mean that that element constitutes a matter of fact which came to light in the course of the procedure. A further requirement is that the party was not in a position to be aware of that matter previously (judgments of 6 July 2000 in *ACIS* v *Parliament*, T-139/99, ECR, EU:T:2000:182, paragraph 62, and of 9 December 2010 in *Tresplain Investments* v *OHIM — Hoo Hing (Golden Elephant Brand)*, T-303/08, ECR, EU:T:2010:505, paragraph 167).

37 Moreover, according to settled case-law, a plea which may be regarded as amplifying a plea put forward previously, whether directly or by implication, in the original application, and which is closely connected therewith, must be declared admissible (judgments of 19 September 2000 in *Dürbeck* v *Commission*, T-252/97, ECR, EU:T:2000:210, paragraph 39; of 28 April 2010 in *Gütermann and Zwicky* v *Commission*, T-456/05 and T-457/05, ECR; EU:T:2010:168, paragraph 199; and of 10 July 2012 in *TF1 and Others* v *Commission*, T-520/09, EU:T:2012:352, paragraph 185).

38 In the present case, it should be noted that the plea put forward by the applicants is not based on any matter of law or of fact which came to light during the procedure within the meaning of the case-law cited at paragraph 36 above.

39 As the applicants themselves confirmed at the hearing, their additional ground for annulment is directed, in essence, at the annulment of the contested decision, on the basis of the contention that it was adopted in breach of Article 3(1)(b) of Regulation No 141/2000, since the medicinal product nilotinib did not meet the criteria laid down in that provision for designation as an orphan medicinal product at the time its marketing authorisation was granted.

40 The inclusion of the medicinal product nilotinib in the Community Register of Orphan Medicinal Products and the marketing authorisation for that product were the subject of Commission decisions of 22 May 2006 and 19 November 2007, respectively.

41 First, the decision designating nilotinib as an orphan medicinal product and the decision to enter it in the Community Register of Orphan Medicinal Products were published, inter alia, on the Commission's website. Moreover, in Article 2 of the Commission's decision concerning that designation, the Commission stated that the EMA would make available to any interested party the COMP's opinion to which that decision refers and which contains the examination carried out by that committee concerning, inter alia, whether nilotinib met the criteria laid down in Article 3(1)(b) of Regulation No 141/2000.

42 Second, the decision authorising the marketing of the medicinal product nilotinib under the commercial name Tasigna was published in summary form in the Official Journal on 28 December 2007 (OJ 2007 C 316, p. 48) and was published in full in the Community Register of Medicinal Products for Human Use, including Annex I to the decision, containing the summary of product characteristics, which includes its pharmacological properties, in particular with regard to its clinical effectiveness by comparison with other existing forms of treatment, and the clinical studies substantiating the claims in respect of those properties.

43 Furthermore, following the decision authorising the marketing of the medicinal product nilotinib under the commercial name Tasigna, several documents relating to the authorisation procedure, including a summary of the COMP's positive opinion on the designation of that product as an orphan medicinal product for the treatment of CML, a summary identifying the different stages of the EMA's examination of the application for marketing authorisation for that product and a document entitled 'Scientific Discussion', were published and updated on the EMA's website. The latter document describes in detail the various parameters taken into consideration by the Committee for Medicinal

Products for Human Use in reaching its recommendation that marketing authorisation should be granted, in particular in relation to the effectiveness and risk/benefit analysis of the medicinal product at issue when compared with existing forms of treatment for the condition in question.

44 Similarly, at the time when the marketing authorisation for nilotinib was granted, the applicants were in a position to apprise themselves of the forms of treatment for CML that had already been authorised, including the medicinal product dasatinib, itself an orphan medicinal product, which had been the subject of two Commission decisions of 3 January 2006 and 20 November 2006 relating, respectively, to the designation of that product as an orphan medicinal product and the authorisation to place it on the market.

45 Moreover, it is common ground that, under Article 5(12) of Regulation No 141/2000, when marketing authorisation is granted for an orphan medicinal product, the requirements laid down in Article 3(1) of that regulation must be fulfilled.

46 Accordingly, even if the applicants were not aware of the two COMP documents before bringing the present action, they must none the less be regarded as having been in a position to apprise themselves of the matters which were taken into account by the competent EMA committees and subsequently by the Commission in concluding that marketing authorisation should be granted for the medicinal product nilotinib as an orphan medicinal product, including matters relating to the condition laid down in Article 3(1)(b) of Regulation No 141/2000 that the medicinal product at issue should be of significant benefit to patients suffering from the condition in question.

47 It should also be noted that the plea alleging infringement of Article 3(1)(b) of Regulation No 141/2000 has no direct connection with the plea in law and arguments relied on by the applicants in the present proceedings and cannot, therefore, be regarded as amplifying a plea already put forward. Indeed, the applicants initially alleged, in support of their application, that the contested decision infringed of Article 8(1) and (3) of Regulation No 141/2000, on the ground that a period of market exclusivity had been granted for the medicinal product nilotinib marketed under the commercial name Tasigna that was independent of the exclusivity granted to the medicinal product Glivec, even though those two medicinal products were regarded as similar products. However, before lodging the reply, the applicants did not plead, either directly or by implication, infringement of Article 3(1)(b) of Regulation No 141/2000 on the ground that the medicinal product nilotinib marketed under the commercial name Tasigna did not meet the criteria for designation as an orphan medicinal product at the time it was authorised and that, accordingly, the EMA was not entitled to rely on it in refusing the applicants' request.

48 Accordingly, as they were not based on matters of law or of fact which came to light in the course of the procedure, the plea alleging infringement of Article 3(1)(b) of Regulation No 141/2000 and all the arguments and objections forming part of that plea must be regarded as new and, therefore, inadmissible under Article 48(2) of the Rules of Procedure.

49 In any event, as regards the objection of illegality put forward by the applicants, in essence, by invoking Article 277 TFEU, as part of their plea, it is appropriate to recall that it is established case-law that Article 277 TFEU gives expression to a general principle conferring on any party to proceedings the right to challenge, as an incidental plea, with a view to obtaining the annulment of a decision of direct and individual concern to that party, the validity of an earlier act of the institutions of general application forming the legal basis of the decision that is being contested, if that party was not entitled under Article 263 TFEU to bring a direct action challenging such an act by which it was thus affected without having been in a position to ask that it be declared void (see, to that effect, judgments of 6 March 1979 in *Simmenthal* v *Commission*, 92/78, ECR, EU:C:1979:53, paragraph 39; of 19 January 1984 in *Andersen and Others* v *Parliament*, 262/80, ECR, EU:C:1984:18, paragraph 6; and of 11 December 2012 in *Sina Bank* v *Council*, T-15/11, ECR, EU:T:2012:661, paragraph 43).

50 Moreover, the objection of illegality cannot be limited to acts in the form of a regulation for the purpose of Article 277 TFEU, in order to ensure that those persons who are precluded from instituting proceedings directly in respect of general acts of the institutions may obtain a genuine judicial review of such acts when they are affected by implementing decision which are of direct and individual concern to them (see, to that effect, judgment in *Simmenthal*, paragraph 49 above, EU:C:1979:53, paragraphs 40 and 41, and judgment of 26 October 1993 in *Reinarz* v *Commission*, T-6/92 and T-52/92, ECR, EU:T:1993:89, paragraph 43).

51 Furthermore, according to case-law, the objection of illegality must be confined to what is essential for the resolution of the dispute and there must be a direct legal connection between the individual decision that is being contested and the general measure in question (see, to that effect, judgments of 31 March 1965 in *Macchiorlati Dalmas* v *High Authority*, 21/64, ECR, EU:C:1965:30, p. 227, 245; of 13 July 1966 in *Italy* v *Council and Commission*, 32/65, ECR, EU:C:1966:42, p. 563, 594; and of 21 February 1984 in *Walzstahl-Vereinigung and Thyssen* v *Commission*, 140/82, 146/82, 221/82 and 226/82, ECR, EU:C:1984:66, paragraph 20).

52 In the present case, the applicants contend that the COMP's summary report of 8 November 2007 and its opinion of 14 November 2007 are unlawful, which contention they repeated at the hearing.

53 It is clear that the COMP's summary report of 8 November 2007 is merely a preparatory measure for its opinion of 14 November 2007, delivered on 14 November 2007 pursuant to Article 5(12) of Regulation No 141/2000 and which, in essence, reiterates the conclusions of that report. The opinion of the committee is in itself one of the preparatory measures for the Commission's decision authorising the marketing of the medicinal product nilotinib under the commercial name Tasigna. It is that Commission decision — which may take a different view from that expressed in the COMP's opinion — that constitutes the act from which the commercial exclusivity enjoyed by that medicinal product is derived and which may be regarded as forming the basis of the contested decision. The committee's opinion and, *a fortiori*, its summary report, do not therefore constitute general acts and are not, by their nature, capable of forming the legal basis of the contested decision or having a direct link with that decision in such a way that their purported illegality may have any effect on the resolution of the present dispute. Accordingly, the objection of illegality raised by the applicants in respect of the COMP's summary report of 8 November 2007 and its opinion of 14 November 2007 must be rejected as inadmissible.

54 It follows from the foregoing considerations that the additional ground for annulment under consideration and all the arguments and objections forming part of that ground must be rejected as out of time under Article 48(2) of the Rules of Procedure and, in any event, inadmissible in so far as concerns the objection of illegality raised under Article 277 TFEU.

The plea alleging infringement of Article 8(1) and (3) of Regulation No 141/2000

55 The applicants submit, in essence, that the EMA erred in law by granting, even though a first authorised orphan medicinal product existed, a new period of exclusivity to a similar second-generation product for therapeutic indications already authorised for the first orphan medicinal product.

56 Article 8(1) of Regulation No 141/2000 provides for only a single ten-year period of market exclusivity to be granted for an orphan medicinal product, it not being possible for the derogations available under Article 8(3) of that regulation to extend that ten-year period. Accordingly, the provisions of Article 8(1) of Regulation No 141/2000 and those of Article 8(3) thereof are mutually exclusive and cannot be applied jointly.

57 Support for that interpretation is to be found, according to the applicants, in the Communication from the Commission on Regulation No 141/2000 (OJ 2003 C 178, p. 2), which indicates that, where a first orphan medicinal product enjoys the benefit of market exclusivity and a second, similar medical product that is safer, more effective or otherwise clinically superior is authorised, the second product shares market exclusivity with the first orphan medicinal product during the remainder of the ten-year period of market exclusivity granted to that first product. *A fortiori*, that principle is applicable where the second orphan medicinal product has simply been authorised on the basis that the holder of the marketing authorisation for the first medicinal product has given his 'consent', in accordance with Article 8(3)(a) of Regulation No 141/2000.

58 The applicants submit, in the alternative, that even if a similar orphan medicinal product authorised under the derogation in Article 8(3) of Regulation No 141/2000 may benefit from an independent ten-year period of market exclusivity, that second period of exclusivity would preclude only authorisation for the marketing of products that are similar to the second orphan product. Such a period of exclusivity cannot operate to prevent marketing authorisation being granted for medicinal products that are similar to the first authorised orphan product, in particular generic versions of that product, after the expiry of the period of market exclusivity attaching to the first orphan product.

59 In support of their interpretation of Article 8(1) and (3) of Regulation No 141/2000, the applicants refer to the objectives pursued by that article, namely the provision of an incentive for investment in the form of a single ten-year period of market exclusivity for the first authorisation of an orphan medicinal product, as indicated in recital 8 in the preamble to that regulation and in the *travaux préparatoires* to the regulation, in particular the Proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products (OJ 1998 C 276, p. 7), put forward by the Commission on 27 July 1998.

60 On the other hand, the interpretation of Article 8 of Regulation No 141/2000 advocated by the EMA could have perverse effects, encouraging sponsors to develop similar medicinal products in order to 'evergreen' the market exclusivity of their existing orphan medicinal products. Thus, in the present case, a generic version of the medicinal product imatinib would be excluded from the market 16 years after marketing authorisation was granted for that product, whereas a medicinal product such as nilotinib, which is considered 50% similar to imatinib and has been developed by the same sponsor, has been granted an independent ten-year period of market exclusivity, even though nilotinib could have benefited in any event from the data protection period provided for by 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).

61 The EMA and the Commission contest those arguments and are of the view that the plea in law in question is unfounded.

62 The plea under consideration raises, in essence, the question whether a medicinal product which, as it is considered liable to be of significant benefit to patients affected by a condition when compared with a similar orphan medicinal product that is already authorised for the same therapeutic indications, is itself designated as an orphan medicinal product may benefit from the market exclusivity provided for in Article 8(1) of Regulation No 141/2000 where the marketing of such a product is approved on the basis of one of the derogations available under Article 8(3) of the regulation, namely where the sponsor of the first medicinal product, who, in the present case, is also the sponsor of the second product, has given his consent.

63 As a preliminary point, it is useful to recall the requirements to be met in order for a medicinal product to be designated as an orphan medicinal product laid down in Article 3(1) of Regulation No 141/2000, namely, first, that the medicinal product is intended for the diagnosis, prevention or treatment of a rare condition or that the marketing of the product would not generate sufficient

return to cover the investment made and, second, that there exists no satisfactory treatment for the condition in question in the EU or, if such treatment exists, that the medicinal product in question will be of significant benefit to patients affected by that condition.

64 Thus, it is clear from the wording of Article 3(1)(b) of Regulation No 141/2000 that a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that it represents a significant benefit to those affected by the condition. In that regard, it is case-law that establishing significant benefit takes place in the context of a comparison with an existing authorised medicinal product or method and cannot be limited to an assessment of the intrinsic qualities of the product in question without comparing them with the intrinsic qualities of the authorised methods (see, to that effect, judgment of 9 September 2010 in *Now Pharm* v *Commission*, T-74/08, ECR, EU:T:2010:376, paragraph 46).

65 It is also apparent from Article 3(1)(b) of Regulation No 141/2000 and the spirit underlying the system established by that regulation that the criteria for a finding of a significant benefit are strict. The development of a medicinal product which is of significant benefit in comparison with the medicinal product already authorised for the treatment of the same condition involves, for the undertaking working on it, investment in research and development of the potential improved medicinal product. An undertaking cannot thus merely develop a similar medicinal product in order to obtain its designation as an orphan medicinal product, marketing authorisation, and the concomitant market exclusivity (see, to that effect, judgment of 9 September 2010 in *CSL Behring* v *Commission and EMA*, T-264/07, ECR; EU:T:2010:371, paragraph 94).

66 Furthermore, the criteria laid down in Article 3(1) of Regulation No 141/2000 must be met, first, where the medicinal product is designated as an orphan product and entered in the Community Register of Orphan Medicinal Products, pursuant to Article 3(1) of the regulation in conjunction with Article 5(9) thereof. Second, those criteria must continue to be met when the medicinal product designated as an orphan product is granted marketing authorisation as an orphan medicinal product since, pursuant to Article 5(12) of the regulation, a medicinal product which, before marketing authorisation is granted, fails to meet the criteria laid down in Article 3(1) of the regulation, must be removed from the register.

67 It should also be recalled that, in accordance with Article 8(1) of Regulation No 141/2000, once marketing authorisation has been granted for an orphan medicinal product, the competent authorities must not, for a period of 10 years, accept another application for a marketing authorisation in respect of a similar medicinal product for the same therapeutic indication or indications included in the designation of the product as an orphan medicinal product.

68 Moreover, Article 8(3) of Regulation No 141/2000 sets out three cases in which, by way of derogation from Article 8(1) of the regulation, the placing on the market of a similar medicinal product may be authorised for the same therapeutic indication as that for which the marketing of an orphan medicinal product has been authorised, notwithstanding the ten-year period of market exclusivity enjoyed by that product. That is the case, inter alia, where the holder of the marketing authorisation for the orphan medicinal product gives his consent to a similar medicinal product being granted marketing authorisation.

69 It is in the light of those observations that the arguments put forward in support of the plea alleging infringement of Article 8 of Regulation No 141/2000 must be examined.

70 In the first place, as regards the applicants' arguments concerning the period of market exclusivity attaching to the medicinal product nilotinib, it is clear that the period established in Article 8(1) of Regulation No 141/2000 for any medicinal product designated as an orphan medicinal product which has marketing authorisation is a period of ten years. An orphan medicinal product, if it remains such a product when it receives marketing authorisation, benefits from market exclusivity which, in

principle, is for a period of 10 years, no provision being made for any extension of that period, which may be reduced, under Article 8(2) of Regulation No 141/2000, only in situations in which it is established that the medicinal product in question no longer meets the requirements laid down in Article 3(1) of the regulation.

71 In the present case, it is apparent from the Commission's decision of 19 December 2007 that authorisation for the marketing of the medicinal product nilotinib under the commercial name Tasigna was granted for that product as an orphan medicinal product, which, in accordance with Article 5(12) of Regulation No 141/2000 implies that, at that time, that medicinal product was still included in the Community Register of Orphan Medicinal Products for the therapeutic indications that were the subject of the application for authorisation and that the requirements laid down in Article 3(1) of the regulation continued to be met. Therefore, pursuant to Article 8(1) of the regulation, once marketing authorisation was granted, that medicinal product benefited from a ten-year period of market exclusivity in so far as concerns the authorised therapeutic indications.

72 In the second place, it is clear that Article 8(3) of Regulation No 141/2000 relates to the marketing authorisation of a similar medicinal product for the same therapeutic indication. That provision sets out the circumstances in which it is possible to derogate from the prohibition laid down in Article 8(1) of the regulation and grant marketing authorisation in respect of such a medicinal product for the same therapeutic indications as those for which an orphan medicinal product enjoys market exclusivity.

73 Article 8(3) of Regulation No 141/2000 has no bearing on the conditions under which marketing authorisation for a 'similar' medicinal product within the meaning of Regulation No 847/2000 may be granted and provides, by way of derogation from Article 8(1) of Regulation No 141/2000, that such a medicinal product may be granted marketing authorisation in three cases, including that in which the holder of the marketing authorisation for the original orphan medicinal product for the same therapeutic indication has given his consent. There is nothing in that provision concerning whether such authorisation confers market exclusivity on a similar medicinal product.

74 As submitted by the EMA and the Commission, a similar medicinal product may itself be an orphan medicinal product or a non-orphan medicinal product. If it is not an orphan product, the marketing authorisation for that product will not confer on it any sort of market exclusivity under Article 8(1) of Regulation No 141/2000. On the other hand, it if is an orphan medicinal product, the ten-year period of market exclusivity with which it is endowed by virtue of Article 8(1) of the regulation cannot be curtailed as a result of the fact that there exists an orphan medicinal product which has received marketing authorisation for the same therapeutic indications and which benefits from market exclusivity for those indications Similarly, the market exclusivity attaching to that product will not be extended as a result of the fact that marketing authorisation has been granted for the second medicinal product. In issue are independent designations as orphan medicinal products and independent marketing authorisations, granted in accordance with separate procedures and triggering separate periods of market exclusivity, which may overlap in time. That is the proper construction of the Communication from the Commission on Regulation No 141/2000, relied on by the applicants.

75 Moreover, Article 8(3) of Regulation No 141/2000 does not establish any order of priority among the three situations where a derogation may be applied under Article 8(1) of that regulation.

76 In the present case, the sponsor of the medicinal product nilotinib cannot be penalised for the fact that it relied on the derogation under Article 8(3)(a) of Regulation No 141/2000 enabling it to obtain the consent of the holder of the marketing authorisation in respect of the original orphan medicinal product for the same therapeutic indications. As that consent was obtained in conformity with that provision, the EMA could only conclude that the derogation available under Article 8(3)(c) of Regulation No 141/2000 applied.

77 Equally irrelevant, for the purpose of the application of Article 8(3) of Regulation No 141/2000, is the fact that the holder of the marketing authorisation for the original orphan medicinal product and the sponsor of the second product are the same pharmaceutical company, as the applicants themselves acknowledged at the hearing.

78 In the third place, contrary to the applicants' contentions, there is nothing in Regulation No 141/2000 to suggest that the application of Article 8(3) precludes the application of Article 8(1). Accordingly, the marketing authorisation granted for an orphan medicinal product in respect of the same therapeutic indications as those for which the original orphan product was authorised, including on one of the grounds laid down in Article 8(3) of Regulation No 141/2000, automatically confers on that product the ten-year period of market exclusivity provided for in Article 8(1) of that regulation.

79 As regards the argument put forward by the applicants in the alternative that, if a second, similar orphan medicinal product which has been granted marketing authorisation for the same therapeutic indications as those for which the marketing of the original orphan product was authorised may benefit from a ten-year period of market exclusivity that is independent of that enjoyed by the original orphan product, that period of exclusivity could operate only to prevent marketing authorisation being granted for products that are similar to the second medicinal product, it is common ground that, under Article 8(1) of Regulation No 141/2000, marketing authorisation may be refused for a 'similar' medicinal product only in respect of the therapeutic indications for which the marketing of an orphan medicinal product has been authorised and in respect of which that orphan product enjoys market exclusivity. By virtue of that provision, market exclusivity attaches to that medicinal product for all those therapeutic indications, irrespective of the fact that the medicinal product in question, which is itself similar to another orphan product which has been granted marketing authorisation, relied on one of the derogations laid down in Article 8(3) of the regulation at the time of that authorisation. Thus, the fact that the therapeutic indications for which both orphan medicinal products received marketing authorisation are similar cannot undermine the market exclusivity enjoyed by each of those medicinal products by virtue of Article 8(1) of that regulation for those therapeutic indications.

80 With regard to the applicants' arguments that the EMA's interpretation is at odds with the objectives pursued by Regulation No 141/2000, specifically Article 8(1) thereof, it must be noted that it is precisely in order to ensure attainment of the objective pursued by the regulation — namely to encourage investment in research, development and marketing of orphan medicinal products — that market exclusivity must be granted in all cases in which an orphan product has been given marketing authorisation. That regulation does not contain any provision under which it is possible not to apply the ten-year period of market exclusivity to orphan medicinal products that have been granted marketing authorisation for certain therapeutic indications, with the exception of the situations set out in Article 8(2) of the regulation, in which the period of exclusivity may be reduced, inter alia if the criteria laid down in Article 3(1) of the regulation are not met. Moreover, that would jeopardise the objective of the regulation in question and run counter to its spirit, as the sponsor of a medicinal product, having made the investment necessary to establish, in procedures for the designation of a product as an orphan medicinal product and marketing authorisation procedures, that the criteria for the designation of its product as an orphan medicinal product have been met, would receive no compensation for such investment.

81 In that regard, contrary to the applicants' contentions, the ten-year period of market exclusivity provided by Regulation No 141/2000 as an incentive for the development and marketing of orphan medicinal products cannot be regarded as equivalent to the data protection periods enjoyed by any medicinal product which has been granted marketing authorisation, as the effects and scope of each of those mechanisms are different.

82 It follows from the above that the plea alleging infringement of Article 8(1) and (3) of Regulation No 141/2000 must be rejected as unfounded.

83 Consequently, the action must be dismissed in its entirety.

Costs

84 Under Article 87(2) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. As the applicants have been unsuccessful, they must be ordered to pay the costs, in accordance with the form of order sought by the EMA.

85 In accordance with the first subparagraph of Article 87(4) of the Rules of Procedure, the institutions which have intervened in the proceedings are to bear their own costs. The Commission must therefore bear its own costs.

On those grounds,

THE GENERAL COURT (Sixth Chamber)

hereby:

1. **Dismisses the action.**

2. **Orders TEVA Pharma BV and Teva Pharmaceuticals Europe BV to bear their own costs and to pay the costs incurred by the European Medicines Agency (EMA).**

3. **Orders the European Commission to bear its own costs.**

Frimodt Nielsen Dehousse Collins

Delivered in open court in Luxembourg on 22 January 2015.

[Signatures]