Case C-602/19

Request for a preliminary ruling

Date lodged:

9 August 2019

Referring court:

Verwaltungsgericht Köln (Germany)

Date of the decision to refer:

9 July 2019

Applicant:

Kohlpharma GmbH

Defendant:

Bundesrepublik Deutschland (Federal Republic of Germany)

Verwaltungsgericht Köln (Administrative Court, Cologne)

Order

In the administrative court proceedings

of the company Kohlpharma GmbH, […] Merzig,

applicant,

[…]

v

Bundesrepublik Deutschland (Federal Republic of Germany), […]

[…]

defendant,

concerning pharmaceutical law (‘Impromen 5 mg’)

the 7th Chamber of the Administrative Court of Cologne

[…]

made the following order:

[Or. 2] The proceedings are stayed […].

The following questions on the interpretation of Articles 34 and 36 TFEU are referred to the Court of Justice of the European Union pursuant to point (a) of the first paragraph and the second paragraph of Article 267 TFEU:

1. Do the principle of the free movement of goods laid down in Article 34 TFEU and the principles, developed on that basis, of the parallel import of medicinal products require the national authorising authority to consent to an amendment to the indications regarding the dosage of a parallel-imported medicinal product even if the reference authorisation has expired and the amendment is substantiated with an adoption of the indications regarding a domestically produced medicinal product with essentially the same active ingredient and different form of administration in combination with the indications approved in the exporting State for the parallel-imported medicinal product?

2. Against the background of Articles 34 and 36 TFEU, can the national authority refuse to consent to such an amendment by noting that parallel importers are exempt from the obligation to submit periodic safety reports and, due to the lack of a domestic reference authorisation, there is no current data on the risk-benefit assessment, the existing domestic authorisation concerns a different form of administration and relates to a different active ingredient concentration from the authorisation for the same form of administration in the exporting State, and the combination of two forms of administration in the information texts is moreover inconceivable?

Grounds

I.

1 On the basis of the judgment of the Court of Justice of 20 May 1976 — Case 104/75 — *De Peijper* [EU:C:1976:67] on the free movement of goods, the applicant is placing a medicinal product in tablet form with national authorisation in Italy by way of ‘parallel import’ on the market in the Federal Republic of Germany. **[Or. 3]**

2 In this respect, by decision of 17 September 1990, the Bundesgesundheitsamt (Federal Health Office; BGA) at that time granted the applicant parallel import authorisation for the prescription-only medicinal product ‘Impromen 5 mg’ in the administration form ‘tablets’ and with the active ingredient ‘bromperidol’ (authorisation No 226.50.00.00). The areas of

application were designated as ‘Certain forms of psychosis requiring treatment with neuroleptics’. The German reference authorisation was that of the medicinal product with the same active ingredient ‘Consilium 5 mg’ (‘Impromen 5 mg’) tablets of the company Janssen GmbH, Neuss, later Janssen-Cilag (authorisation No 1156.01.01). The parallel import concerned the medicinal product ‘impromen’ tablets of the company Prodotti Formenti S.r.l., Milan. (marketing authorisation holder: Grunenthal Italia S.r.l.) that is authorised (authorisation No 026017020) and on the market in Italy. The applicant provided the German authorising authority with written assurance that the import would exclusively concern the medicinal product placed on the market by that pharmaceutical trader in Italy. The parallel import authorisation was granted, subject to the adjustment to future amendments to the German reference authorisation, in 1990 and extended in 2002. The texts of the use and expert information were adjusted to those of the reference authorisation here. A further extension application made in 2005 remained unresolved.

3 In Germany, ‘Consilium 5 mg’ (‘Impromen 5 mg’) in tablet form was recently likewise authorised for application in the case of certain forms of psychosis requiring treatment with neuroleptics. Authorisation was also granted for the administration form ‘drops’. The reference authorisation holder recently used combined expert information for both forms of administration. According to the defendant, the last batch of that medicinal product in tablet form was placed on the market in Germany on 30 June 2007. The use and expert information was last updated on 20 April 2005. The reference authorisation expired on 30 June 2010. Since then, that preparation has only appeared in drop form on the market in Germany, whereas both drops and tablets of ‘impromen’ have national authorisation and are on the market in Italy. According to unchallenged information from the defendant, the medicinal product in tablet form is not authorised in any Member State of the Union other than Italy. **[Or. 4]**

4 In the period that followed, the applicant informed the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices; BfArM) of amendments to the texts of the use and expert information for the medicinal product at issue in implementation of the results of the ‘antipsychotics’ graduated plan decision.

5 On 30 November 2015 the applicant informed the BfArM, under Paragraph 29 of the German Arzneimittelgesetz (Law on pharmaceuticals, AMG), inter alia of amendments to the use and expert information regarding the dosage of the imported tablet preparation. The following was stated under point 4.2 of the expert information:

‘Dosage’

The daily dose must be determined on an individual basis. The lowest still effective initial oral dose should be given. The optimum maintenance dose is generally 1-10 mg; for the intake of a smaller or specific amount of bromperidol,

the administration form IMPROMEN drops (*not currently in the Kohlpharma range) is available (on average 5 mg corresponding to 1 tablet), once daily.

Titration

As the antipsychotic effect can be assessed as early as 24 hours after administration, the titration up to the effective dose can take place on a day-to-day basis. This makes it possible to achieve the desired effects within around 3 days.

Dose adjustment

The dose can be increased by a maximum of 10 mg per week, in which case a maximum daily dose of 50 mg may not be exceeded.

When the desired effect is achieved, the dose is reduced by 10 mg per week down to the lowest dose which maintains the desired effect.

[…]

Subacute and chronic schizophrenia

1 x daily 2-3 ml solution (corresponding to 4-6 mg bromperidol). In this case, the administration form IMPROMEN drops (*not currently in the Kohlpharma range) is available if required or a tablet is to be taken daily for a dosage of 5 mg bromperidol.

Dosage for older patients

The dose should be halved for older patients. **[Or. 5]**

Children and adolescents

[…]

Application type

IMPROMEN 5 mg tablets should be taken in a single daily dose, generally after the evening meal, in the dose fixed by the doctor, with some liquid.

[…]’

6 The use information was worded accordingly. The texts were based on an adoption of the sense of the current dosage indications for the drops authorised in Germany.

7 In Italy, the same texts are used for drops and tablets. The use information there reads as follows:

'Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

La dose raccomandata e da 1 mg a 15 mg al giorno, con una dose media ottimale dio 5 mg al giorno. II medico stabilirà la dose adatta a lei, compatibilmente con la sua condizione e la sua reazione al trattamento.

Prenda le gocce o le compresse una volta al giorno.

Per Impromen gocce orali soluzione, la dose di 5 mg e equivalente a 11 gocce.'

According to the translation submitted by the applicant:

'Always take this medication exactly as discussed with your doctor or pharmacist. Ask your doctor or pharmacist in case of uncertainty.

The recommended daily dose is between 1 mg and 15 mg, with an optimum average daily dose of 5 mg. Your doctor will determine the dose that is suitable for you, in relation to your constitution and depending on the success of the treatment.

Take the drops or tablets once daily. **[Or. 6]**

Impromen solution, oral drops: the dose of 5 mg corresponds to 11 drops.'

8 By letter to the applicant of 25 February 2016, the BfArM informed it that the indicated amendments to the dosage under Paragraph 29(2a) of the AMG were not approved. It had already been repeatedly stated that the parallel import authorisation had been granted subject to constant adjustment to the reference authorisation. It was known that such an adjustment had not been possible for years. The applicant was now seeking a remedy through adoption of the texts for 'Impromen drops 2 mg/ml' of the company Eumedica. This was impossible, as clearly shown by the texts communicated, since it was possible to start the treatment at ½ ml = 1 mg with the drops, whereas tablets could only be started at 5 mg. The individual dose adjustment was not possible in the same way with the tablets. In addition, the dosage for chronic and subacute schizophrenia and for older people could not be realised with tablets. 'Impromen drops 2 mg/ml' was not the reference authorisation. The attempt at adjustment was regulatorily impossible.

9 The applicant filed an opposition against that decision. The adjustment related to a product with the same active ingredient and comprised the transfer of the indications for the drops to the administration form 'tablets'. In addition, the application was left to the doctor's decision and it was to be assumed that the tablets were used for patients whose condition was already being managed. The preparation constituted a significant and established alternative application.

10 By opposition decision of 1 July 2016, the BfArM rejected the applicant's opposition as unfounded. The authority referred to the reasoning in the initial decision. It also stated that, by referring to the other administration form 'drops', the applicant created uncertainty and reduced compliance. This was precisely not compatible with the need for pharmaceutical safety in the case of a medicinal product for the treatment of schizophrenia.

11 The applicant brought an action on 1 August 2016. **[Or. 7]**

12 The wording indicated was based on a consultation of the German text and alignment with the Italian texts for 'Impromen tablets'. Warning information from the manufacturer of the medicinal product authorised in Germany in drop form had also been adopted here. The BfArM was obliged to consent to the notification of amendment and could not refer to the fact that, when treatment was started, the dosage for the tablets was 5 times higher than for drops. The standard dosage was the same for the two administration forms at 5 mg/day. Reference was expressly made to the drops available in Germany for smaller amounts. The respective dosage was left to the doctor, who could prescribe the drops, should a more precise dosage be required.

13 The refusal of consent was also incomprehensible because it meant that the product was on the market with out-of-date texts. It — the applicant — had fulfilled its responsibility, by having adjusted the use information texts used in Italy to the more stringent specifications for the drops in Germany. The authority obviously considered the tablets to present a risk overall following the expiry of the reference authorisation.

14 An individual dosage was also possible with the tablets, as they had a break groove. As the mode of operation of drops and tablets did not differ, the same use information was used for both in Italy. It was also recognised by the case-law of the Court of Justice that expiry of the reference authorisation did not lead to the expiry of the parallel import authorisation granted. It was instead up to the parallel importer to make the necessary adjustments and obtain the corresponding information.

15 In the present proceedings, the applicant requested that,

> with annulment of the BfArM's decision of 25 February 2016 in the form of the opposition decision of 1 July 2016, the defendant be obliged to consent to the notification of amendment of 30 November 2015 with regard to the dosage.

16 The defendant requested that

> the action be dismissed. **[Or. 8]**

17 It does not concur with the applicant's arguments and states the following. The sale of the medicinal product no longer corresponds to the parallel import

authorisation model. The authorisation for the parallel-imported medicinal product was granted subject to adjustment to future amendments to the reference authorisation. The amendment indicated cannot be such an adjustment, as a reference authorisation no longer exists. There is no parallel to the drops authorised in Germany. The product 'Impromen drops, 2 mg/ml solution' (authorisation number 1156.00.02) has a completely different administration form and therefore also a different dosage. With parallel imports too, the change of administration form leads to the reauthorisation obligation under Paragraph 29(3), first sentence, point 2 of the AMG. In addition, the information texts used in Italy and the texts used for the drops in Germany have considerable differences. The concentrations of the active ingredient are also different for the drops. While it is 10 mg/ml in the Italian authorisation, it is 2 mg/ml in the German. Finally, the combination of two administration forms in one set of use information is inconceivable.

18 The individual dose adjustment is impossible with the tablets and is also not guaranteed by the break groove that is present, especially since no data exists on breaking strength and division accuracy. As parallel importers are exempt from the obligation to submit periodic safety reports (PSURs) pursuant to the second sentence of Paragraph 63d(6) of the AMG, there is also no current data on the risk-benefit assessment for the preparation in tablet form.

19 At the hearing on 9 July 2019, the parties concerned reaffirmed their different views.

20 […] **[Or. 9]**

II.

21 The proceedings are to be stayed and, pursuant to point (a) of the first paragraph and the second paragraph of Article 267 TFEU, referred to the Court of Justice of the European Union for interpretation of the scope of Article 34 TFEU in consideration of the case-law of the Court of Justice on the requirements for authorisations of the parallel import of medicinal products by way of a preliminary ruling.

22 The applicant has a parallel import licence for the medicinal product 'Impromen 5 mg' tablets granted by the Bundesinstitut für Arzneimittel- und Medizinprodukte (BfArM) as competent higher federal authority in the simplified procedure. This was granted subject to adjustment to future amendments to the domestic reference authorisation. However, that authorisation expired on 30 June 2010.

23 The Court of Justice has repeatedly stated that it follows from Article 34 TFEU that a Member State must not obstruct parallel imports of a medicinal product by requiring parallel importers to satisfy the same requirements as those which are applicable to undertakings applying for the first time for a marketing authorisation for a medicinal product.

24 The Court of Justice has also ruled that the existence of the parallel import licence is fundamentally independent of the further existence of the domestic reference authorisation. According thereto, national legislation under which the withdrawal of the marketing authorisation of reference for a medicinal product at the request of its holder means that the parallel import licence automatically ceases to be valid is incompatible with the principle of the free movement of goods (judgment of 10 September 2002 — Case C-172/00 — *Ferring* [EU:C:2002:474], judgment of 8 May 2003 — C-15/01 — [*Paranova Läkemedel and Others*, EU:C:2003:256], paragraph 46). This primarily refers to the case of the waiver of the reference authorisation or the case of relevance here of its expiry due to passage of time. However, that is subject to the condition that the import of the parallel-authorised medicinal product does not undermine the effective protection of the life and health of humans within the meaning of Article 36 TFEU (most recently for the case of the parallel import of a generic medicinal product: judgment of 3 July 2019 — C-387/18 — [*Delfarma*, EU:C:2019:556]). **[Or. 10]**

25 The referring court does not currently see sufficient indications of a risk to the effective protection of the life and health of humans within the meaning of Article 36 TFEU. The defendant pointed out that the dosage schedule for the drops contained specifications which were not achievable with tablets. It also emphasised that parallel importers were released from the obligation to submit periodic safety update reports (PSURs) and the drops authorised in Germany had a different active ingredient concentration to the drops authorised in Italy.

26 Against this background, the question arises as to the possibilities and requirements for amending a parallel import licence after expiry of the domestic reference authorisation. In the opinion of the referring court, such amendments are not excluded from the outset and are to be assessed according to the same standards as apply to the granting of a parallel import licence. They would have to be rejected if one of the grounds for refusal mentioned in Article 26 of Directive 2001/83/EC applies. As, however, there is no domestic reference authorisation, it is questionable under which criteria a subsequent amendment by the parallel importer can be substantiated.

27 The applicant in the present proceedings substantiates the amendment of the dosage indications for the parallel-imported tablets with a partial adoption of the indications for the drops that are still authorised in Germany and alignment with the texts for the tablets that are authorised in Italy. This procedure is rejected by the defendant on the ground that it is contrary to the regulatory concept of parallel imports.

28 In this case, the authorising authority applies the national provision of Paragraph 29(2a) of the AMG to the amendment to the parallel import licence. This reads as follows:

‘A change

1. in the indications under Paragraphs 10, 11 and 11a on the dosage, the type or duration of the application, the areas of application, if this does not concern the addition or modification of an indication which is to be classified under another **[Or. 11]** area of treatment, a limitation of the contra-indications, side effects or interactions with other substances,

2. in the active constituents, excluding the medically active constituents,

3. in an administration form comparable with the one authorised,

3a. […]

4. in connection with considerable changes in the manufacturing process, the administration form, the specification or the impurity profile of the active ingredient or the medicinal product that may have a clear effect on the quality, safety or efficacy of the medicinal product, […]

5. in the package size, and

6. […],

may only be made if the competent higher federal authority has granted its approval. […] The approval shall be deemed to be granted if no objection to the change has been filed within a period of three months.'

29 Paragraph 11(1), point 4, of the AMG reads as follows:

'Finished medicinal products which are medicinal products within the meaning of Paragraph 2(1) or Paragraph 2(2), point 1, and which are not […] exempted from the authorisation obligation may only be placed on the market in the scope of this law with a package leaflet which bears the heading 'Use information' and must contain the following indications in the order below in easily legible, readily comprehensible German and in conformity with the indications under Paragraph 11a: **[Or. 12]**

4. the instructions required for proper application, relating to

a) dosage,

b) type of application,

c) frequency of administration, specifying if necessary the exact time at which the medicinal product may or must be administered,

and, if required and depending on the nature of the medicinal product,

d) duration of treatment, if this should be fixed,

e) advice in the event of an overdose or omitted doses, or advice on the risk of adverse consequences if the treatment is stopped,

f) the express recommendation that the doctor or pharmacist should be consulted in the event of queries relating to the application;

…'

30 Paragraph 11a(1), sentence 1 and sentence 2, point 4(b), of the AMG reads as follows:

'The pharmaceutical trader shall be obliged to make available on request to doctors, dentists, veterinarians, pharmacists […] use information for experts (expert information) for finished medicinal products which are subject to the authorisation obligation or exempted from authorisation, […]. This must bear the heading 'Expert information' and contain the following indications in clearly legible lettering in conformity with the summary of the medicinal product's characteristics approved in the context of the authorisation and in the following order:

…

4. clinical indications

…

b) dosage and type of administration for adults and, in so far as the medicinal product is intended for administration to children, for children, **[Or. 13]**

…'

31 If the authority intends to refuse consent to a notification of amendment, it shall bear the burden of explanation and proof in respect of the existence of grounds for rejection […].

32 In that case, the criteria for the decision are the grounds for refusing to grant authorisation listed in the first sentence of Paragraph 25(2) of the AMG. Points 1 and 2 of the provision read as follows:

'The competent higher federal authority may refuse authorisation only if

1. the documents submitted, including such documents as are to be submitted pursuant to a regulation of the European Community or the European Union, are incomplete,

2. the medicinal product has not been sufficiently tested in accordance with the confirmed state of scientific knowledge in each case or the other scientific information material under Paragraph 22(3) does not correspond to the confirmed state of scientific knowledge in each case,

3. …’

33 The questions that are set out in the operative part of the order and are relevant to the decision in the present dispute cannot be answered with sufficient certainty on the basis of the previous case-law of the Court of Justice of the European Union and by interpretation of Articles 34 and 36 TFEU having regard to Directive 2001/83/EC, and are therefore to be referred to the Court of Justice for a preliminary ruling.

[…]