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Datasheet for the decision of 2 March 2021

Case Number: T 1418/15 - 3.3.01

Application Number: 04766541.9

Publication Number: 1658073

IPC: A61K31/44, A61J3/00

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL PRODUCT FOR INJECTION

Patent Proprietor:
Takeda GmbH

Opponents:
Gallafent, Antony Xavier
Actavis Group PTC ehf
Isarpatent Patent- und Rechtsanwälte
Generics [UK] Limited

Headword:
Pantoprazole for injection/TAKEDA

Relevant legal provisions:
EPC Art. 54, 56

Keyword:

Novelty - main request (yes)
Inventive step - all requests (no) - obvious alternative

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Beschwerdekammern

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Case Number: T 1418/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 March 2021

Appellant 1: (Opponent 1)	Gallafent, Antony Xavier EuGen IP Limited 21 Bridge Street Llandeilo SA19 6BN (GB)
Appellant 2: (Opponent 2)	Actavis Group PTC ehf Reykjavikurvegi 76-78 220 Hafnarfjördur (IS)
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Representative:	Isarpatent Patent- und Rechtsanwälte Behnisch Barth Charles Hassa Peckmann & Partner mbB Friedrichstrasse 31 80801 München (DE)
Appellant 4: (Opponent 4)	Generics [UK] Limited Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)

Respondent: (Patent Proprietor)	Takeda GmbH Byk-Gulden-Strasse 2 78467 Konstanz (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 May 2015 concerning maintenance of the European Patent No. 1658073 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. The appeals by each of opponents 1-4 (appellants 1-4, respectively) lie against the opposition division's interlocutory decision that European patent No. 1 658 073 in the version of the main request and the invention to which it related met the requirements of the EPC.

Claim 1 of the main request reads as follows:

"*1. Pharmaceutical product for injection comprising a container including a closure suitable for preparations for injection, the container containing a compound selected from the group of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (pantoprazole), a salt thereof, a solvate of pantoprazole and a salt thereof, wherein the container and closure are made of material which essentially does not release zinc ions, whereby the closure is a rubber stopper of type 1 according to European Pharmacopoeia 2002, wherein the amount of extractable zinc from the closure is 0 ppm (i.e. not detectable), when determined according to European Pharmacopeia 2002, and wherein the product comprises a clear glass vial fitted with said rubber stopper and a crimp seal.*"

II. The following documents are referred to in the present decision.

D1 Summary of product characteristics. Protium i.v., January 2000

D2 Label of Protonix® I.V., FDA, 2001

D3 WO 02/41919

D6 European Pharmacopoeia, Supplement 2000, 136-137

D11 EP 0 841 374

D17 Formula characteristics of PH 21/50 Gray, West Pharmaceutical Services

D24 DE 4324014

D32 Certificate of analysis of PH 701/40/OW/winered/ weinrot/lie, West Pharmaceutical Services

D35 Declaration from West Pharmaceutical Services dated 12 January 2015

III. Four oppositions had been filed against the patent. The opposition proceedings were based on the grounds of Article 100(c), (b) and (a) EPC for lack of novelty and inventive step.

IV. In the decision under appeal, the opposition division held among other things that the subject-matter of claim 1 was novel over the content of documents D1-D3 and D24 and that it was inventive starting from document D3 as the closest prior art.

V. With their statements of grounds of appeal, appellants 1-4 raised objections with respect to the issues of sufficiency of disclosure, novelty and inventive step. Appellants 3 and 4 also raised objections of added subject-matter.

VI. With its reply to the statements of grounds of appeal, the patent proprietor (respondent) requested that the appeals be dismissed. Alternatively, it requested that the patent be maintained in amended form on the basis of the claims filed on 12 January 2015 as the auxiliary request (auxiliary request 1).

Claim 1 of auxiliary request 1 differs from claim 1 of the main request by the addition of the feature "*wherein a rubber for the stopper was manufactured without the use of zinc-containing components*".

VII. Appellants 2 and 3 reacted to the respondent's reply to the statements of grounds of appeal.

VIII. Third-party observations were filed on 9 February 2018 and 14 June 2018.

IX. The respondent replied to appellants 2 and 3 and the third-party observations.

X. The board scheduled oral proceedings in line with the parties' requests and gave its preliminary opinion.

XI. By letter dated 11 December 2019, the respondent filed the claims of auxiliary request 2.

Claim 1 of auxiliary request 2 is identical to claim 1 of the main request except for the parentheses around the feature "i.e. not detectable", which have been deleted.

XII. Appellants 2 and 3 and the respondent made further submissions before the oral proceedings.

XIII. Oral proceedings were held on 2 March 2021 in the absence of appellants 1 and 4, who had previously informed the board that they would not attend.

XIV. The appellants' arguments, where relevant to the present decision, can be summarised as follows.

The subject-matter of claim 1 of the main request was not novel over the stoppered glass vials containing lyophilised pantoprazole sodium for injection disclosed in documents D1 and D2. The respondent had submitted in its reply to the notices of opposition (see letter dated 29 November 2013, page 7, section V.3.2) that the stoppers in D1 and D2 were those analysed in document D32 and that their content of extractable zinc was 0.4 ppm. The feature in claim 1 that the amount of extractable zinc from the closure was "0 ppm (i.e. not detectable)" could not render the claimed product novel. On the one hand, the feature "i.e. not detectable" was not limiting because it was in parentheses. On the other hand, applying the conventional interpretation of whole numbers and rounding-off rules, "0 ppm" covered any amount below 0.5 ppm. This was consistent with the expression in claim 1 "essentially does not release zinc ions", which allowed the presence of an undetermined amount of releasable zinc. The description could not be used to modify the meaning of the features in claim 1.

Documents D3 and D24 also anticipated the product in claim 1 of the main request. Although the documents did not explicitly disclose their stoppers, it could be assumed that they were free of zinc.

The product in claim 1 of the main request was not inventive starting from any of documents D1-D3. If novel, the claimed product differed in that its rubber stopper had lower amounts of releasable zinc. The respondent's allegation that this difference resulted

in a lower level of particle formation upon reconstitution of the pantoprazole solution had not been proven. The comparative tests filed on 11 May 2009 did not show a direct link between the lower amount of releasable zinc in the rubber stopper and the lower level of particle formation because the composition of the stoppers had not been specified and their differences were unknown. It was apparent from their different colours that the stoppers did not differ only in their content of extractable zinc (see comparative tests filed on 11 May 2009, table at the bottom of page 2). The wine-red colour of the stopper in D1 was very likely produced by an inorganic pigment containing traces of metals other than zinc which could also interact with pantoprazole. The respondent had neither shown that the particles formed resulted from the interaction of zinc with pantoprazole since no analysis of the particles had been made. Therefore, the objective technical problem was the provision of an alternative pharmaceutical product. The skilled person would have arrived at the product of claim 1 since it would have been obvious to chose any alternative rubber stopper, i.e. any stopper of type 1 according to European Pharmacopoeia, as suggested in D6. Such alternative rubber stoppers were for instance disclosed in D11 and D17. These stoppers did not contain any releasable zinc and, in the case of D17, were commercially available at the relevant date (see respondent's reply to the statements of grounds of appeal, page 10, paragraph 2; and D35).

For the same reasons, the subject-matter of claim 1 of each of the auxiliary requests also lacked inventive step.

XV. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

The subject-matter of claim 1 of the main request was novel over the content of documents D1-D3 and D24 because none of these documents disclosed the zinc content of their rubber stoppers. The stoppers in D1 and D2 contained 0.4 ppm of extractable zinc, as shown in D32. This amount was not encompassed by the feature in claim 1 "0 ppm (i.e. not detectable), when determined in accordance to the European Pharmacopoeia 2002" because 0.4 ppm could be detected in accordance with that method. Claim 1 had to be read in a technically reasonable manner and in light of the description. The patent taught (see column 3, lines 3-9, and column 2, lines 14-19) that the amount of extractable zinc in the stopper was 0 ppm and that this meant that the amount was not detectable, i.e. it was below the detection limit. There was no basis in the patent to conclude that 0 ppm could mean any value below 0.5 ppm because the application defined 0 ppm as meaning not detectable. The number 0 could not be interpreted as being merely a whole number obtained after rounding off.

The pharmaceutical product in claim 1 of the main request was inventive. Starting from any of D1-D3, the difference was the lower zinc content in the rubber stopper of the product in claim 1. The tests filed in November 2008 at the oral proceedings before the examining division showed that the product of document D1 produced precipitates upon reconstitution of the solution for injection. The comparative tests filed on 11 May 2009 showed that a lower zinc content in the rubber stopper reduced the formation of undesired zinc-pantoprazole particles in the reconstituted solution.

All tested products had a rubber stopper of type 1 according to European Pharmacopoeia 2002. In the comparative examples, the rubber stopper was from D1 (grey cap), while in the examples according to claim 1, the rubber stopper had no detectable amounts of extractable zinc (blue cap). The observed effect could be assigned to the lower zinc content since it was reasonable to assume that zinc was the only component in the rubber stoppers that had an action on pantoprazole. Other ingredients such as the rubber material and the colour did not lead to the problem of particle formation. The opposition division decided to accept this argument, and the appellants failed to prove that this decision was wrong. Therefore, the objective technical problem was the provision of a pharmaceutical pantoprazole product for injection with improved stability (lower level of particle formation). Even if the technical effect shown by the tests of 11 May 2009 was not acknowledged and the problem was formulated as the provision of an alternative pantoprazole product for injection, the subject-matter of claim 1 was still inventive. The appellants' arguments that the skilled person would have used a different stopper were tainted with hindsight; even if the skilled person could have used another stopper, there would have been no reason to do so. The closest prior art could be combined only with a document dealing with pantoprazole since the objective technical problem was specifically linked to the stability of pantoprazole. However, the cited prior art did not teach the use of any other rubber stopper for pantoprazole products.

For the same reasons, the subject-matter of the auxiliary requests was also inventive.

XVI. The parties' final requests as far as relevant to the present decision were as follows.

- Appellants 1 to 4 requested that the decision under appeal be set aside and that the patent be revoked.
- In addition, appellant 2 requested that auxiliary request 2 not be admitted into the appeal proceedings.
- The respondent requested that the appeals be dismissed, i.e. that the patent be maintained in amended form on the basis of the main request underlying the decision under appeal or, alternatively, that the patent be maintained in amended form on the basis of the claims of auxiliary request 1 filed with the letter dated 12 January 2015 or, further alternatively, on the basis of the claims of auxiliary request 2 filed with the letter dated 11 December 2019.

XVII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeals are admissible. They meet the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Claim 1 of the main request - novelty (Article 54 EPC)

The appellants considered that the pharmaceutical product of claim 1 was anticipated by those disclosed in documents D1-D3 and D24.

2.1 It was common ground that D1 and D2 disclose a pharmaceutical product for injection consisting of a glass vial fitted with a rubber stopper and a crimp seal which contains freeze-dried pantoprazole sodium (see D1, sections 2 and 6.5; D2, section "Description", paragraph 3).

D1 and D2 do not disclose the amount of zinc releasable from their rubber stoppers. However, in the opposition proceedings, the respondent submitted (see letter dated 29 November 2013, page 7, section V.3.2) that it was the owner of the products in D1 and D2 and provided the certificate of analysis D32 which showed that, according to European Pharmacopoeia 2002, the stoppers of D1 and D2, referred to as PH701/40/OW/winered, were of type 1 and released 0.4 ppm zinc (see D32, second line, and "Soluble Zinc" entry in the table). This was not contested by the appellants.

The matter of dispute in relation to the issue of novelty over D1 and D2 was whether the amount of releasable zinc of 0.4 ppm was encompassed by the feature in claim 1 "0 ppm (i.e. not detectable), when determined according to European Pharmacopoeia 2002". This feature was already present in claim 1 as granted.

The appellants considered that the expression in parentheses was not limiting and that, following the common rules for rounding off, 0 ppm meant any amount lower than 0.5 ppm, i.e. it included 0.4 ppm. The respondent argued that, in view of the general teaching in the application as filed, 0 ppm was an amount that could not be detected using the methods specified in European Pharmacopoeia 2002. As 0.4 ppm was detectable (see D32), the products of D1 and D2 were not according to claim 1.

The board concurs with the appellants that the expression "i.e. not detectable" in claim 1 cannot be considered limiting because it appears in parentheses. It also concurs that 0 ppm in claim 1 does not imply an absolute absence of releasable zinc. The claim indicates that the closure essentially does not release zinc ions and that it is a rubber stopper of type 1 according to European Pharmacopoeia 2002 (i.e. it releases a maximum of 5 ppm, see D32, "Soluble zinc" entry, middle box). Thus, the rubber stopper of claim 1 may release zinc to a certain extent around 0 ppm, but it is unclear how far from 0 ppm the released amount may be. The board is nevertheless not convinced that 0 ppm automatically means any amount which results in 0 ppm after rounding off, i.e. any amount lower than 0.5 ppm.

In such a situation, where the scope of claim 1 is unclear and the combination of features which gives rise to the lack of clarity was already present in the granted claims, clarification may be sought in the description of the patent.

A general reading of the patent conveys the teaching that the gist of the invention lies on the fact that the rubber stopper of the claimed product essentially does not release zinc ions. The passage on column 3, lines 3-9, of the patent discloses that a closure material which essentially does not release zinc ions is a material having an amount of extractable zinc of 0 ppm and clarifies that this means that the amount is not detectable by the methods specified in European Pharmacopoeia 2002.

Thus, considering that the amount of releasable zinc from the rubber stoppers of D1 and D2 is 0.4 ppm and that this amount is detectable by the method of European Pharmacopoeia 2002 (see D32), the board concludes that the products in D1 and D2 do not fall within the definition of claim 1.

2.2 D3 and D24 disclose the preparation of freeze-dried pantoprazole sodium solutions for injection, but they are silent on the amount of releasable zinc from the rubber stopper of the container (see D3, page 2, paragraph 2, and examples; and D24, column 1, lines 51-54, and column 2, lines 27-30). Appellant 3's statement that it could be assumed that the documents inherently disclose the use of zinc-free stoppers is an unsupported allegation.

2.3 Therefore, the board holds that the subject-matter of claim 1 is novel. Claim 1 thus complies with Article 54 EPC.

3. *Claim 1 of the main request - inventive step (Article 56 EPC)*

The patent concerns (see paragraphs [0007] and [0008]) a pharmaceutical pantoprazole product for injection contained in a clear glass fitted with a rubber stopper and a crimping seal. This kind of product was known and commercially available at the relevant date, e.g. as "Protonix® i.v.". Such products contain pantoprazole in lyophilised form and, before use, they are reconstituted with a carrier solution for injection. The problem in the prior art products was that upon reconstitution of the solution, particles were formed. As injectable solutions must be free of particles, there was the need to avoid particle formation.

3.1 It was common ground among the parties that any of D1-D3 was a suitable starting point for the assessment of inventive step. D1 and D2 disclose commercially available freeze-dried pantoprazole products for injection contained in a clear glass vial fitted with a rubber stopper and a crimping seal. D1 and D2 disclose the commercial products Protium® i.v. and Protonix® i.v., respectively. D3 concerns similar products but is not so specific in the description of its container. As the container is a decisive element in the case at hand, the board considers each of D1 and D2 to represent the closest prior art.

3.2 The respondent submitted in its reply to the notices of opposition dated 29 November 2013 (see page 7, section V.3.2) that it had issued documents D1 and D2 and that the rubber stoppers of the vials disclosed in them were those analysed in D32. These stoppers had a content of extractable zinc of 0.4 ppm according to European Pharmacopoeia 2002.

This was not contested by the appellants, who concurred that the pharmaceutical product of claim 1 differed from those in D1 and D2 in the lower content of extractable zinc of the rubber stoppers.

3.3 According to the respondent, the comparative tests filed on 11 May 2009 proved that this difference resulted in a lower formation of particles upon reconstitution of the solution for injection. They showed (see first table on page 1, table at the bottom of page 2 and table on page 3) that a product with a rubber stopper as in D1 (grey cap) resulted in more particle formation than a product with a rubber stopper according to claim 1 (blue cap).

The board disagrees. As noted by the appellants, the comparative tests do not allow unequivocally attributing the lower level of particle formation to the lower levels of extractable zinc because the compared rubber stoppers differ not only in their levels of extractable zinc but also in other features such as their colour.

The exact composition of the stoppers is unknown, and the respondent has not provided it. Neither has the respondent provided evidence showing that the particles formed essentially result from a pantoprazole-zinc interaction. It is, however, apparent from the different colours of the rubber stoppers that they have different compositions and that this difference very likely involves the presence of traces of metal ions which, like zinc ions, may interact with pantoprazole. For instance, the wine-red colour of the stopper in D1 (see D32) may be produced by an inorganic pigment containing metals other than zinc. Therefore, it cannot be concluded that the lower particle formation in the product according to claim 1 results from the lower content of releasable zinc.

Therefore, the objective technical problem has to be formulated as the provision of an alternative pantoprazole product for injection.

3.4 The exchange of the rubber stopper in the product of D1 or D2 with any other rubber stopper of type 1 according to European Pharmacopoeia 2002 was an obvious modification for the skilled person trying to provide alternative products since type 1 rubber stoppers were the ones preferably used for pharmaceutical freeze-dried powders and aqueous parenteral preparations at

the relevant date of the patent (see D6, page 4, left-hand column, last sentence). Such rubber stoppers included the one in D17 (PH 21/50 GRAY). This stopper has 0.0 ppm extractable zinc and was commercially available at the relevant date of the patent (see D35). Another obvious alternative was the rubber stopper for medical solutions disclosed in D11 (see page 1, lines 7-13; page 2, line 57, to page 3, line 5; and Table 2). It fulfilled the standards of the pharmacopoeias of Japan, the United States and various European countries and was made without using zinc compounds.

Hence, the skilled person would have arrived at the claimed subject-matter by exchanging the rubber stopper of the products in D1 or D2 with one from D17 or D11.

3.5 The respondent argued that the exchange of the rubber stopper was based on hindsight because other features of the products in D1 and D2 could have been modified in the search for alternatives. It also argued that the document to be combined with the closest prior art had to be directed specifically to pantoprazole products.

These arguments are not convincing. First, the fact that the skilled person could have modified the products of the prior art in several ways does not render the modification proposed in claim 1 inventive; it remains an obvious modification that the skilled person would have routinely carried out when searching for alternatives. Second, D6 relates to rubber closures for containers for pharmaceutical preparations of the same kind as in claim 1. Such rubber closures are taught as being generally applicable, and the skilled person had no reason to believe that they would not be suitable for pantoprazole-based products. The rubber stopper of D17 is a type 1 closure, the preferred

closure type according to D6. The rubber closures in D11 were also of that type.

3.6 In conclusion, the subject-matter of claim 1 does not involve an inventive step, and claim 1 does not meet the requirements of Article 56 EPC.

4. *Claim 1 of auxiliary requests 1 and 2 - inventive step (Article 56 EPC)*

The respondent did not provide inventive step arguments beyond those already submitted in relation to the main request. The reasons the product of claim 1 of the main request is not inventive apply also to claim 1 of auxiliary requests 1 and 2.

The product of claim 1 of auxiliary request 1 differs from the one in claim 1 of the main request in that the rubber stopper was manufactured without the use of zinc-containing components. The product of claim 1 of auxiliary request 2 is essentially the same as the one in claim 1 of the main request. In both cases, the claimed product differs from the closest prior art in that its rubber stopper has lower amounts of releasable zinc. As with the main request, there is no evidence that this difference provides any effect. So the objective technical problem remains the provision of an alternative product. Likewise, the skilled person would have arrived at the product of claim 1 of each of auxiliary requests 1 and 2 by replacing the rubber stopper of D1 or D2 with one from those in D17 or D11, which contain no extractable zinc. Thus, claim 1 of each of auxiliary requests 1 and 2 does not meet the requirements of Article 56 EPC either.

5. Appellant 2 had requested that auxiliary request 2 not be admitted into the appeal proceedings. In view of the outcome of the assessment of inventive step in relation to this request (see point 4 above), the board sees no need to provide reasons for its decision to admit the request into the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

M. Schalow A. Lindner

Decision electronically authenticated