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Datasheet for the decision of 11 April 2013

Case Number: T 1422/12 - 3.3.10

Application Number: 07776245.8

Publication Number: 2016045

IPC: C07C 237/26, C07C 231/24

Language of the proceedings: EN

Title of invention:
Tigecycline crystalline forms and processes for preparation thereof

Applicant:
TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Headword:
Tigecycline crystalline forms/TEVA

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes): (re)formulation of technical problem allowable - any effects may be taken into account, so long as they concern the same field of use and do not change the character of the invention"
"Specific crystalline form of tigecycline non-obvious over amorphous form in view of the unexpected improvement in stability with respect to epimerisation specific to this type of tetracycline antibiotic"

Decisions cited:
T 0440/91, T 0039/93, T 0013/84, T 0777/08

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1422/12 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 11 April 2013

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 20 January 2012 refusing European patent application No. 07776245.8 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: P. Gryczka
Members: J. Mercey
F. Blumer

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division refusing European patent application No. 07776245.8 with the European publication No. 2 016 045 and International publication No. WO 2007/127292.

II. Claim 1 of the set of twenty claims underlying the contested decision (present sole request) read as follows:

"A crystalline form of Tigecycline characterized by a powder XRD pattern having peaks at 6.8, 9.5, 9.8, 12.1, 12.6, 18.1, 20.2, 21.6, 23.3, and 26.8 ± 0.2 degrees 2-theta."

III. *Inter alia* the following documents were cited in the examination proceedings:

(1) WO 2006/128150,
(2) US-A-5 675 030 and
(3) Threlfall T. L., "Analysis of Organic Polymorphs, A Review", Analyst, London, GB, vol. 120, October 1995, pages 2435 to 2460.

In the decision under appeal, the Examining Division considered that the product of Example 8 of document (2) represented the closest prior art and held that the problem to be solved by the invention was merely the provision of an alternative solid form of tigecycline, reformulation of the problem to the provision of a more thermodynamically stable form of tigecycline not being allowable, since thermodynamic stability was not

mentioned in the application as filed. Since it was known that crystalline forms of drugs were easier to handle and more stable upon storage, the skilled person would have attempted to crystallise the amorphous form of tigecycline, citing document (3) to show that a large number of marketed drugs present polymorphism. Therefore, the claimed subject-matter did not involve an inventive step.

IV. In a communication dated 16 January 2013 pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal, the Board drew attention to the contradictory statements on file with regard to the nature of the product of Example 8 of document (2), namely as to whether it was amorphous or crystalline, and to the decision T 777/08 (OJ EPO 2011, 633), relating to the inventiveness of a crystalline *vis-à-vis* the amorphous form of a pharmaceutically active compound.

V. At the oral proceedings before the Board held on 11 April 2013, the Appellant (Applicant) submitted a main request, the claims of which corresponded exactly to those underlying the contested decision.

The Appellant submitted that the tigecycline product of Example 8 of the closest prior art document (2) was indeed amorphous, as originally stated in the application as filed. Further confirmation of the amorphous nature of the product of Example 8 of document (2) was provided by the declaration:

(5) Declaration of Subodh Deshmukh dated 18. October 2010 filed before the USPTO during prosecution of the US application corresponding to document (1),

and by the further repetition of the process of Example 8, the experimental details of which were submitted as Annex B with letter dated 8 March 2013. Starting from the amorphous form of tigecycline disclosed in document (2), the problem to be solved by the application in suit was the provision of tigecycline which was more stable with respect to epimerisation. It submitted that the formulation of the technical problem in this manner was allowable, since improved stability was derivable from paragraphs [0009] and [0010] of the application as filed. Said problem was successfully solved, since the comparative data submitted before the Examining Division and filed again with letter dated 23 May 2012 showed that under storage conditions at 40°C, the claimed crystalline form was significantly more stable than the amorphous material with regard to the unwanted degradation to epi-tigecycline. No motivation was provided in document (2) alone, or in combination with document (3), to solve said problem by providing a particular crystalline form of tigecycline. On the contrary, document (3) taught away from the present invention, and the fact that tigecycline was already marketed in the amorphous form suggested that previous routine attempts to screen for crystalline forms had been unsuccessful.

VI. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request as filed during the oral proceedings before the Board.

VII. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Inventive Step*

2.1 The sole issue arising from this appeal is the inventiveness of the subject-matter of the claims of the main request on file.

2.2 The Board considers, in agreement with the Examining Division and the Appellant, that the closest prior art is document (2), more particularly, the product of Example 8 thereof, which is a solid form of tigecycline. According to the Appellant (see page 5, paragraph [0024] and X-ray diffractogram of Figure 1 of the application as filed), repetition of Example 8 of document (2) resulted in amorphous tigecycline. A further repetition of the process of Example 8 performed by the Appellant, the experimental details of which were provided in Annex B of letter dated 8 March 2013, confirmed said conclusion. With regard to the Appellant's submission to the Examining Division in the letter dated 22 March 2010 that a repetition of the procedure of this example resulted in a *crystalline* form of tigecycline, the Appellant subsequently provided the full experimental protocol which resulted in this assertion, namely Annex A accompanying its letter dated 8 March 2013. Said procedure was, however, not a true repetition of the

prior art, since the requirements that the pH of the mixture obtained at column 13, line 30 of Example 8 of document (2) was adjusted to 7.2 to 7.4 and that the solution was stirred in a chill room overnight (see column 13, lines 31 to 33), were not fulfilled. This divergence from the prior art procedure could have influenced the nature of the final product, such that this "repetition" is to be disregarded when assessing the nature of the product of Example 8 of document (2). Further confirmation that the product of Example 8 of document (2) is amorphous is also provided in the form of the declaration (5) submitted by one of the inventors cited in document (1) before the USPTO. The Board is thus convinced that the tigecycline product of Example 8 of document (2) is an amorphous material.

2.3 In view of this state of the art, the Appellant submitted that the problem underlying the present application is the provision of tigecycline which is more stable with respect to epimerisation.

2.3.1 In the decision under appeal, the Examining Division did not accept the formulation of the technical problem as the provision of tigecycline in more thermodynamically stable form, since there was no indication in the application as filed that this was indeed the problem which the invention attempted to solve. The reference in paragraph [0010] of the application to the chemical and physical stability of crystalline solids was very general and belonged merely to the background of the invention and thus could not form a basis for formulating the problem.

2.3.2 According to the well established case law of the Boards of Appeal, the technical problem has to be determined on the basis of objectively established facts, since for the determination of the objective technical problem, only the effect actually achieved *vis-à-vis* the closest prior art should be taken into account (see T 13/84, Headnote I and points 10 and 11, OJ EPO 1986, 253 and T 39/93, points 5.3.1 to 5.3.4, OJ EPO 1997, 134). In this connection, any effects may be taken into account, so long as they concern the same field of use and do not change the character of the invention (see T 440/91, points 4.1 and 4.2, not published in OJ EPO).

2.3.3 In the present case, it is indicated in the application in suit (see page 1, paragraphs [0002], [0003] and [0004]) that the present invention relates to crystalline forms of tigecycline, tigecycline being a tetracycline antibiotic already marketed as lyophilised powder or cake for intravenous injection, namely in the amorphous form. The section concerning the background of the invention (see pages 2 to 4, paragraphs [0007] to [0011]) relates to improving the performance characteristics of pharmaceutical products, including tigecycline. The formulation of the technical problem to be solved as the provision of tigecycline which is more stable with respect to epimerisation, said reduction in epimerisation resulting in improved biological activity, thus falls within the framework of the invention as disclosed in the application in suit, namely the performance characteristics of the antibiotic, tigecycline, regardless of whether these characteristics are relevant to handling, storage or formulation and/or to its pharmaceutical properties.

That the more *specific* problem of improved stability with respect to epimerisation is not mentioned in the application as originally filed is irrelevant (see T 39/93, point 5.3.5, *loc. cit.*), since improvement of stability by avoidance of epimerisation, and, as a consequence, improved biological activity, is clearly recognisable by the skilled person as a desirable effect for a tetracycline antibiotic. As a consequence, the Board does not agree with the conclusions of the Examining Division regarding the formulation of the technical problem and thus allows the definition given under point 2.3 above.

2.4 As the solution to this problem, the application proposes a crystalline form of tigecycline according to claim 1, which is characterised by a specific powder XRD pattern.

2.5 It now needs to be examined whether said problem has been successfully solved. With letter dated 23 May 2012, the Appellant filed comparative data showing that under storage conditions at 40°C, the claimed crystalline form is significantly more stable than the amorphous material with regard to the unwanted degradation to epi-tigecycline. More particularly, when exposing the amorphous form of tigecycline with epimer content of 0.13% to these conditions, the epi-tigecycline increased to 4.83% after a month, whereas the level of epimer in the claimed crystalline form remained insignificant even after 6 months (0.10% at t=0, 0.10% after 3 months and 0.18% after 6 months). The Board thus holds that it is credible that the problem underlying the application in suit has been successfully solved.

2.6 Finally, it remains to be decided whether or not the proposed solution to this objective problem is obvious in view of the state of the art.

2.6.1 Document (2) teaches (see column 1, lines 27 to 36) that all tetracyclines, to varying degrees, epimerise at the 4-position of the D ring with resultant decrease in antibacterial activity. Document (2) itself attempts to solve this problem by devising specific purification methods (see column 1, lines 39 to 62 and claims 1 and 13). Neither this document, nor any other document on file suggests that the problem of instability of tetracycline antibiotics, let alone that caused by epimerisation, could be solved by going from the amorphous to a specific crystalline form.

2.6.2 The facts of the present case are clearly distinguishable from those leading to the decision T 777/08 (*loc. cit.*) which stated (see Headnote I) that **"in the absence of any unexpected property**, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step" (emphasis added). Thus whereas in that case it was regarded that "When starting from the amorphous form of a pharmaceutically active compound as closest prior art, the skilled person would have a clear expectation that a crystalline form thereof would provide a solution to the problem of providing a product having **improved filterability and drying characteristics**" (see Headnote II, emphasis added), in the present case the problem was that of providing a product which is more stable with respect to epimerisation. Whereas in the

case leading to the decision T 777/08, prior art was available teaching that in the pharmaceutical industry crystalline products were generally regarded as the easiest to isolate, purify, dry, handle and formulate, in the present case, there is no prior art teaching that the problem of epimerisation of tetracyclines may be solved by crystalline forms thereof, such that this property may be regarded as unexpected, the problem of epimerisation being very specific to tetracyclines.

Thus although document (3) teaches (see paragraph bridging pages 2452 and 2453) that "Amorphous solids are always less stable than crystalline forms", said paragraph concerns polymers and inorganic glasses and hence this teaching cannot be transferred to the field of tetracycline antibiotics, let alone to the specific problem of epimerisation thereof. Indeed document (3) itself (see page 2453, paragraph bridging left and right hand columns) addresses the problem of amorphous organic materials in the pharmaceutical industry, particularly antibiotics, stating that they have long been used in the amorphous form because of the difficulty of crystallisation and solubility problems of the crystalline forms. Said paragraph goes on to state that "More recently attention has been paid to the deliberate use of amorphous forms with a crystallization inhibitor as a means of more rapid drug delivery". In the present case, at the filing date of the application in suit, tigecycline was indeed already on the pharmaceutical market in the amorphous form, namely as lyophilised powder or cake (see paragraph [0004] on page 1 of application in suit). Thus document (3) cannot be considered to disclose a general teaching to use a crystalline form of an antibiotic in order to

improve its chemical stability, let alone of a tetracycline with respect to epimerisation.

2.7 Accordingly, there is no suggestion in document (2), or in any of the prior art cited, to prepare a crystalline form of tigecycline, in order to improve its stability with respect to epimerisation.

2.8 For these reasons, the Board concludes that the specific crystalline form of tigecycline according to claim 1, and by the same token a process for preparing said crystalline form according to independent claim 10, a pharmaceutical formulation comprising said crystalline form of independent claim 18, and said crystalline form for treating a mammal suffering from infections of independent claim 20, together with the subject-matter of dependent claims 2 to 9, 11 to 17 and 19, involves an inventive step within the meaning of Articles 52(1) and 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 20 of the main request as filed during the oral proceedings before the Board and a description yet to be adapted.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka