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Datasheet for the decision of 9 May 2023

Case Number: T 0437/21 - 3.3.07

Application Number: 14155218.2

Publication Number: 2774606

IPC: A61K9/00, A61K9/20, A61K9/28, A61K31/55, A61P9/10

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition comprising ivabradine hydrochloride polymorph IV

Patent Proprietor:
Synthon B.V.

Opponents:
Dr. Schön, Neymeyr & Partner Patentanwälte mbB
Neidlein, Helga
Maiwald GmbH
Strawman Limited
Algemeen Octrooi- en Merkenbureau B.V.

Headword:
Pharmaceutical composition comprising ivabradine hydrochloride polymorph IV / SYNTHON B.V.

Relevant legal provisions:
EPC Art. 100(a), 56

Keyword:
Inventive step - problem invention (no) - obvious solution

Decisions cited:
T 0252/10, T 0843/91, T 1518/11, T 1033/04

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Case Number: T 0437/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 May 2023

Appellant: (Patent Proprietor)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
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Respondent: (Opponent 1)	Dr. Schön, Neymeyr & Partner Patentanwälte mbB Bavariaring 26 80336 München (DE)
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Representative:	Algemeen Octrooi- en Merkenbureau B.V. P.O. Box 645 5600 AP Eindhoven (NL)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 March 2021 revoking European patent No. 2774606 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	L. Basterreix

Summary of Facts and Submissions

I. Five oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed. Opponent 4 withdrew its opposition during the first instance proceedings.

II. The appeal was filed by the patent proprietor (appellant) against the decision of the opposition division to revoke the patent.

The decision was based on the patent as granted as the main request, on auxiliary requests 1 and 2 filed on 15 May 2020, and on auxiliary requests 3 and 4 submitted during oral proceedings on 1 February 2021.

III. Claim 1 of the patent read as follows:

"A tablet composition comprising ivabradine hydrochloride polymorph IV, wherein the X-ray powder diffraction pattern of polymorph IV comprises characteristic peaks at the following 2 theta (± 0.2) angles: 8.8°, 15.6°, 17.1°, 19.9°, 24.2° and 24.5°, measured using a Cu Kα radiation, characterized in that the composition is stabilized by a moisture barrier with a WVTR of less than 0.01 g/m^2/day at 38°C/90% RH created by means of packaging the tablet in blister pack material and wherein the tablet is an immediate-release tablet."

Claim 1 of auxiliary request 1 was identical to granted claim 1.

Claim 1 of auxiliary request 2 differed by the addition of the feature: "whereby the composition comprises pharmaceutically acceptable excipients, chosen from one or more binders, diluents, disintegrants, glidants, lubricants, stabilizers, surface active agents or pH-adjusting agents".

Claim 1 of auxiliary request 3 differed from granted claim 1 in that the ivabradine HCl polymorph IV was specified to be a hemihydrate.

Claim 1 of auxiliary request 4 differed from granted claim 1 in that the ivabradine HCl polymorph IV was specified to be a hemihydrate and to show a XRPD pattern as reproduced therein.

IV. The following documents among others were cited in the appealed decision:

D2: WO 2013/064307 A1
D3: WO 2011/098582 A2
D11: Pilchik, R., "Pharmaceutical Blister Packaging, Part I", Rationale and Materials, Pharmaceutical Technology November 2000, p 68-76
D15: WO 2013/017582 A1
D18: EMEA ICH Topic Q1A (R2) - “Stability Testing of new Drug Substances and Products”, EMEA, August 2013
D24: Stability experiment carried out on tablet formulations of ivabradine hydrochloride (Form IV) according to Example 26 of D2
D32 “WHO Expert Committee on Specifications for Pharmaceutical Preparations" Thirty-fourth report of 1996, p 1-194

V. The opposition division decided that the criteria of inventive step were not met. In particular, starting from the use of ivabradine HCl form IV in immediate-release tablets reported in D2, the subject-matter of claim 1 of the main request differed in that the composition was "stabilized by a moisture barrier with a WVTR of less than 0.01 g/m^2/day at 38°C/90% RH created by means of packaging the tablet in blister pack material". The technical problem was to provide another immediate-release tablet ivabradine HCl formulation suitable for marketing purposes, or simply to provide an alternative package for a known ivabradine HCl dosage form. The claimed solution was obvious in light of D11, D15 and D3.

The subject-matter of auxiliary requests 1 and 2 likewise lacked an inventive step. Auxiliary requests 3 and 4 were not admitted into the proceedings.

VI. With their statement setting out the grounds of appeal, the appellant defended their case on the basis of the patent as granted as the main request, and on the basis of the same auxiliary requests 1-4 as underlying the decision under appeal (see III. above).

The appellant additionally filed D37:

D37: Xin-Bo Zhou, Acta Cryst. 2019, C75, 545-553.

VII. Opponents 1, 2, 3 and 5 (respondents 1, 2, 3 and 5) each filed a reply to the appeal.

VIII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA 2020.

IX. By letter dated 7 March 2023, the appellant made further submissions. In reply, by letter dated 6 April 2023, respondent 1 filed D38:

D38: J. F. Bauer, Pharmaceutical Solids, Journal of Validation Technology, 2008, pages 15-23

X. Oral proceedings took place before the Board on 9 May 2023. At the end of the oral proceedings, the Board announced the decision to dismiss the appeal.

XI. By letter dated 15 May 2023, the appellant stated that they withdrew the appeal.

XII. The parties' requests are the following:

(a) The appellant requests that the decision under appeal be set aside and that the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-4.

(b) Respondents 1, 2, 3 and 5 each request that the appeal be dismissed.

The respondents further request not to admit into the proceedings auxiliary requests 3 and 4 (respondents 1, 3 and 5), D37 (respondents 1 and 3), and the new arguments filed on 7 March 2023 by the appellant (respondent 1).

XIII. The appellant's arguments regarding inventive step over D2 may be summarised as follows:

D2 disclosed ivabradine HCl form IV, and represented a suitable starting point for the assessment of inventive

step. D2 described form IV as stable, and did not raise any doubt about its long-term stability. For the purpose of registering a pharmaceutical product, the stability of the active ingredient within the pharmaceutical composition generally needed to be examined. However, there were no instructions that the finished products should be tested specifically for the polymorphic stability of the active ingredient, and there were no instructions that such tests should be conducted under stress conditions for extended periods of time. As shown in D24, observing the instability of ivabradine HCl form IV as part of a pharmaceutical composition was not straightforward. Hence, the problem underlying the present invention would not have been observed as part of the skilled person's routine, and was hitherto not recognized in the art.

The technical problem was the provision of a stabilized pharmaceutical composition of ivabradine HCl form IV. The claimed solution involved an inventive step. While blister packaging was the most common approach in the pharmaceutical industry, there was no motivation to apply more complex materials providing an improved moisture-barrier to compositions comprising ivabradine HCl form IV, because this polymorphic form was known as stable over long storage periods. The identification of a suitable package material that prevented the polymorphic conversion of ivabradine HCl form IV was not obvious.

XIV. The respondents' arguments regarding inventive step over D2 may be summarised as follows:

Starting from the use of ivabradine HCl form IV in immediate release tablets shown in D2, the subject matter of claim 1 of the main request differed by the

blister pack material with a moisture barrier having a WVTR of less than 0.01 g/m^2/day at 38°C/90% RH.

The claimed subject-matter did not involve an inventive step since Al/Al blister packaging was well known in the art for the packaging of moisture sensitive drug products, as evidenced by D11, and had been applied for the same active ingredient ivabradine HCl in D3 and D15.

The claimed subject-matter did not qualify as a problem invention. D2 did not describe form IV as the thermodynamically most stable polymorphic form of ivabradine HCl. Furthermore, the testing of the drug product for storage stability was required for marketing approval of a pharmaceutical product such as the claimed tablet composition. Thus the average skilled person would anyway have had to address this problem by routine testing.

Reasons for the Decision

1. Procedural matters

The appellant stated by letter dated 15 May 2023 that the appeal was withdrawn. However, since the decision to dismiss the appeal had been announced at the oral proceedings held on 9 May 2023 and thereby became effective on that day, the appeal proceedings are terminated (T 843/91 of 17 March 1993, OJ EPO, 1994, 818, point 10 of the reasons). Given that by virtue of the board's decision the revocation became final, and that any petition for review would have no suspensive effect, the appellant's submission made after the

announcement of the board's decision is without any legal effect.

Furthermore, a statement of withdrawal of the appeal made by the (sole) appellant after the final decision of the board has been announced at oral proceedings does not relieve the board of its duty to issue and notify to the appellant the decision in writing setting out the reasons for the decision (T 1033/04, point 3 of the reasons; T 1518/11, point 2 of the reasons).

2. Admittance of the new arguments filed on 7 March 2023 by the appellant

Respondent 1 requested that the new arguments filed by the appellant by letter dated 7 March 2023 (specifically, those in the last paragraph on page 3 of the letter) not be admitted into the proceedings. During the oral proceedings, the Board decided to admit these arguments, as well as document D38 filed in response by respondent 1. Considering that the appellant's arguments do not modify the Board's assessment of inventive step (see below), it is not necessary to detail the reasons for their admittance.

3. Main request (patent as granted), inventive step

3.1 The patent pertains to an immediate-release tablet composition comprising ivabradine HCl polymorph IV. According to the patent, polymorph IV, especially in pharmaceutical compositions, transforms overtime into the more stable polymorph ß, in particular in humid environments. The problem underlying the invention is thus to provide pharmaceutical compositions comprising ivabradine HCl polymorph IV which are stable and suitable for use on a commercial scale (see paragraphs

[0003]-[0004] of the patent). This problem is solved, following claim 1, by stabilizing the tablet by a moisture barrier as claimed, created by means of packaging the tablet in blister pack material.

3.2 D2 discloses the use of ivabradine HCl form IV to obtain immediate release tablets (see page 5, lines 35-36, and example 26 on page 17). The polymorph IV referred to in D2 exhibits the same XRPD pattern as defined in claim 1 of the main request (see D2, page 6, lines 19-22). There is no debate that D2 is a suitable starting point for the assessment of inventive step.

3.3 Differentiating features

The subject-matter of claim 1 of the main request differs from the teaching of D2 in that the composition is stabilized by a moisture barrier with a water vapor transmission rate (WVTR) of less than 0.01 g/m^2/day at 38°C/90% RH created by means of packaging the tablet in blister pack material.

3.4 Technical effect and problem

According to the appellant, the objective technical problem is the provision of a stabilized pharmaceutical composition of ivabradine HCl form IV. The appellant relies on paragraphs [0025]-[0028] of the patent in support.

Paragraphs [0025]-[0028] of the patent compare the stability, at 40°C and 75% RH for periods of 2.5 to 6 months, of ivabradine HCl form IV tablets (uncoated and coated) in different blister pack materials. It is found that the use of a cold form foil (CFF, or Alu-Alu foil), which has a WVTR value within the claimed range

(see paragraph [0015]), prevents the conversion of form IV into form ß. In contrast, the use of blister pack materials with lesser moisture barrier properties, i.e. higher WVTR values (PVC, Duplex) leads to partial conversion into form ß.

The Board concludes that a technical effect of stabilizing form IV against conversion into form ß in tablets under such humid conditions is credibly shown. The technical problem may be formulated as the appellant suggests, namely as the provision of a stabilized pharmaceutical composition of ivabradine HCl form IV, at least to the extent that the stability refers to this stability against this polymorphic conversion.

3.5 Does the claimed invention qualify as a "problem invention"?

According to the appellant, D2 describes form IV as stable. The problem of instability of ivabradine HCl form IV as part of a pharmaceutical composition would not have been observed as part of the skilled person's routine and was hitherto not recognized in the art.

The Board does not share this view.

3.5.1 D2 firstly discusses general aspects of polymorphic behavior of drugs (see page 4, second paragraph). The document differentiates between the most stable polymorphic form and metastable forms, and mentions that the transformation of metastable polymorphs to the stable polymorph may be facilitated by moisture (see page 4).

D2 then emphasizes the need to produce ivabradine HCl Form IV in "a form having constant physical properties", and indicates that form IV is "a thermodynamically stable polymorphic form *under certain experimental conditions of isolation or purification*" (see page 5, *emphasis* added by the Board). The skilled person would not understand this qualified statement as indicating that form IV is the most stable polymorphic form of ivabradine HCl. The further statement of D2 that ivabradine HCl form IV is "stable and easy to handle" (see page 5, lines 8-14) also does not teach that form IV is perfectly stable.

D2 does not teach either that form IV is perfectly stable when formulated in a tablet. In particular, in example 26 (see page 17), the description of the process for preparing a tablet comprising ivabradine HCl form IV is followed by the conclusion "The absence of any transformation of the crystalline Form IV of ivabradine hydrochloride was confirmed". This statement does not refer to storage stability or stability upon exposure to moisture, and would rather be read as referring to stability during the preparation steps.

Thus, there is no teaching in D2 that ivabradine HCl form IV is perfectly stable, whether as such or formulated in a tablet.

3.5.2 An inventive step may, in certain circumstances, be acknowledged on the basis of the discovery of an unrecognised problem, even if the claimed solution is in itself obvious (see also the Case Law of the Boards of Appeal, 10th edition, 2022, I.D.9.12). However, the posing of a problem which the skilled person would have encountered in the course of routine work cannot represent a contribution to the inventive merit of a

claimed subject-matter. It is therefore not sufficient that the prior art is silent about a problem for the claimed invention to qualify as a problem invention. As explained in T 252/10 (point 8 of the reasons), the absence of a hint in the prior art that there might still be a desire for further improvement does not mean that an unrecognized problem has been discovered.

In the case at hand, D2 neither says whether the stability over time of ivabradine HCl form IV in a tablet formulation may or may not be improved. However, the skilled person would in any case have had to address the stability issues of formulated form IV as part of routine works towards development of the tablet for commercial use.

This is because, as acknowledged by the appellant, and as explained in D2 (see the paragraph bridging pages 4 and 5), for the purpose of registering a pharmaceutical product, the stability of the active ingredient within the pharmaceutical composition needs to be examined in any case. It is also part of the common general knowledge that not only the drug substance (here: ivabradine HCl form IV) but also the finished dosage forms (here: immediate release tablets containing it) must be tested for stability and constant physical properties (see D32, annex 5 on page 65; see also the guidance D18, 1.3 and 2.2.1). Thus the skilled person would in any case have to verify the stability of the immediate-release tablet comprising ivabradine HCl polymorph IV, irrespective of any statements regarding its stability or lack thereof in the prior art D2. In addition, considering the emphasis on ivabradine HCl solid state polymorphism in the closest prior art D2, there is no doubt that the skilled person would have tested the finished products specifically for

polymorphic stability. This is supported by the common general knowledge reflected in D38 (see page 20, right column: "Product stability studies should assure there are no polymorphic changes during the product shelf life of the commercial package").

The appellant did not demonstrate that observing the instability of ivabradine HCl form IV in a pharmaceutical composition would have required any undue effort. On the contrary, the post-published evidence D24 shows that, when subjecting the tablets of example 26 of D2, containing ivabradine HCl form IV, to the standard stress conditions 40°C / 75% RH for a month, a complete loss of form IV is observable. Contrary to the appellant's position, the use of such accelerated stability testing conditions is not uncommon and is recommended in D32 (see Annex 5).

Consequently, the Board does not consider that the present situation qualifies as a problem invention. The technical problem formulated above (see 3.4) would have been posed by the person skilled in the art starting from D2.

3.5.3 Obviousness

It was part of the common general knowledge to package moisture sensitive drug products in Al/Al blister packaging (see D11, page 77, "Cold-formed foil/foil"). Such a blister pack material affords a WVTR below 0.01 g/m^2/day at 38°C/90% RH according to the patent (see paragraph [0015]). The use of Al/Al blister packaging as gas exchange non-permeable packaging in the context of ivabradine HCl is also disclosed in D3 (see the paragraph bridging pages 14-15, and examples 24-27) or D15 (see page 26, lines 21-25).

Accordingly, the skilled person, seeking to address the above stability problem arising under humid conditions, would consider using such a blister pack material as a solution. The choice of this obvious solution to the technical problem does not involve an inventive step, irrespective of any other routes which the skilled person might also have explored.

In conclusion, addressing shortcomings of finished drug products in terms of stability belongs to the normal activities of the person skilled in the art. Starting from D2 and faced with the stability issues of the immediate-release tablet comprising ivabradine HCl polymorph IV shown therein, the skilled person would turn to blister pack material as defined in claim 1 in order to solve the problem.

In conclusion, the main request does not meet the criteria of inventive step.

4. Auxiliary requests 1-4

The amendments introduced in auxiliary requests 1-4 have no bearing on the issue of inventive step over D2.

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request.

Claim 1 of auxiliary request 2 additionally mandates that the composition comprises commonly known pharmaceutically acceptable excipients. The choice of these broadly defined excipients is not shown to result in any particular technical effect and does not involve any inventive step.

Neither the limitation of ivabradine HCl polymorph IV to a hemihydrate in claim 1 of auxiliary request 3, nor the XRPD pattern introduced in claim 1 of auxiliary request 4, constitute any additional difference over the identical form IV of D2.

Accordingly, none of the auxiliary requests 1-4 satisfy the requirements of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated