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Datasheet for the decision of 24 August 2021

Case Number: T 1869/16 - 3.3.07

Application Number: 10184115.3

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IPC: A61K9/16, A61K9/24, A61K31/4184, A61K31/5415, A61K9/28, A61K9/50

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition comprising hydrochlorothiazide and telmisartan

Patent Proprietor:
LEK Pharmaceuticals d.d.

Opponent:
isarpatent - Patentanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB

Headword:
Telmisartan/LEK PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 54, 56

Keyword:

Novelty - (yes)
Inventive step - unexpected improvement shown

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Beschwerdekammern

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Case Number: T 1869/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 24 August 2021

Appellant: (Opponent)	isarpatent - Patentanwälte Behnisch Barth Charles Hassa Peckmann und Partner mbB Friedrichstrasse 31 80801 München (DE)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Patent Proprietor)	LEK Pharmaceuticals d.d. Verovskova 57 1526 Ljubljana (SI)
Representative:	Prüfer & Partner mbB Patentanwälte · Rechtsanwälte Sohnckestraße 12 81479 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 June 2016 rejecting the opposition filed against European patent No. 2269583 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 2 269 583 (hereinafter "the patent") was granted on the basis of fourteen claims.

The independent claim 1 as granted related to:

"A pharmaceutical composition comprising at least one first unit, selected from granules, pellets, or tablet cores; wherein said first unit comprises first active pharmaceutical ingredient together with pharmaceutically acceptable excipients and at least one coating comprising a second active pharmaceutical ingredient applied onto said first unit, where the second active pharmaceutical ingredients is 6-chloro-3,4-dihydro-2H-1,2,4-benzotiadiazine-7-sulfonamide-1,1-dioxide and unit comprising the other active pharmaceutical ingredient is characterized in that said unit alone imparts pH above 8 to the 1 % by weight aqueous solution or dispersion of said other unit, where said unit comprises 2-[4-[[4-methyl-6-(1-methylbenzoimidazol-2-yl)-2-propyl-benzoimidazol-1-yl]methyl]phenyl] benzoic acid or a salt thereof as the other active pharmaceutical ingredient."

Independent claim 12 of the patent as granted defined:

"A process for manufacturing a pharmaceutical composition characterized in that the first units are manufactured comprising 2-[4-[[4-methyl-6-(1-methylbenzoimidazol-2-yl)-2-propyl-benzoimidazol-1-yl]methyl]phenyl] benzoic acid or its salt; onto those units an optional separating coating is applied; and a coating comprising 6-chloro-3,4-dihydro-2H-1,2,4-

benzotiadiazine-7-sulfonamide-1,1-dioxide is applied thereto."

The agent in the core unit is hereinafter referred to as telmisartan and the agent in the coating is hereinafter referred to as HCT.

II. The patent was opposed on the grounds that it did not sufficiently disclose the claimed invention, that the claimed subject-matter lacked novelty and that the claimed subject-matter lacked an inventive step.

The appeal was filed by the opponents (hereinafter: appellants) against the decision of the opposition division to reject the opposition.

III. In the present decision, reference is made to the following documents submitted before the opposition division:

D1: WO03/059327
D4: WO2005/039639
D7: US2005/0004107
D14: WO2006/063737
D23: Modern Pharmaceutics, 4th Edition, Chapter 10 "Tablet Dosage Forms", pages 287,318-324
D24: Pharmaceutics. The Science of Dosage Form Design, 2nd Edition, Chapter 28 "Coating of tablets and multipariculates", pages 441, 442, 446
D25: Test report "Telmisartan Hydrochlorothiazide FCT 80mg/12.5mg - Dissolution Study", Burjak and Berglez, 13 September 2012
D31: Experimental Data and expert opinion with regard to EP2269583B1, Dr. Muños Ruiz, 15 April 2016

D32' : Sandoz, "Telmisartan+Hydrochlorothiazide" (annexed to the minutes of the oral proceedings before the opposition division).

and the following document submitted during the appeal proceedings:

D35 : Sandoz, "Telmisartan+Hydrochlorothiazide" (identical to D32')

IV. In the contested decision the opposition division came to the following conclusions:

(a) The content of document D32' was not considered relevant and was not taken into consideration for the decision.

(b) The patent sufficiently disclosed the claimed invention.

(c) The subject-matter defined in the patent as granted was new in view of documents D1, D7 and D14. The claims defined a composition comprising a unit containing telmisartan and a coating containing HCT. The coating was to be understood as a layer around the central unit. Documents D1 and D14 described bilayer tablets made of two contiguous layers, but failed to describe a surrounding layer as in a coating. Document D7 described matrix tablets obtained by compression of mixture of separate telmisartan containing granules and HCT containing granules, wherein HCT would not be present in a layer.

(d) Document D1 represented the closest prior art describing tablets comprising telmisartan and HCT in separate layers of a compressed bilayer tablet, from which the claimed subject-matter differed in that the HCT was contained in a coating around a telmisartan unit.

The information on file did not allow for the conclusion that this difference was associated with an advantage in terms of initial impurities and degradation upon storage or enabled the concomitant release of the active agents. A particular ease of manufacture had not been demonstrated and did anyway not represent a surprising effect of the difference with document D1. The problem to be solved was therefore to find an alternative pharmaceutical form for telmisartan and HCT which keeps these agents separate.

Even though documents D23 and D24 described coated tablets as possible systems for co-formulating chemically incompatible materials, the formulation design of the claims as granted would not be obvious as solution in view of a vast choice of options, the lack of a relevant pointer in the prior art and the mention of unsuccessful approaches involving coated HCT in document D1.

V. In the statement setting out the grounds of appeal the appellant contested the findings of the opposition division regarding novelty in view of documents D1 and D7 and inventive step in view of document D1 as closest prior art.

VI. With the reply to the appeal the respondent (patent proprietor) submitted *inter alia* document D35 and

reproduced the experimental results as filed before the opposition division with the letter of 19 April 2016 (see reply page 16).

VII. With the summons of 29 July 2020 the parties were invited to attend oral proceedings to be held on 17 September 2021.

In its communication pursuant to Article 15(1) RPBA 2020 of 26 November 2020 the Board expressed *inter alia* its preliminary opinion that

- document D35 was to be admitted into the appeal procedure (see section 2.2),

- documents D1 and D7 did not anticipate the subject-matter of the claims of the patent as granted ,

- the respondent had plausibly argued why the diverging data in document D31 did not compromise the results presented in the patent, the reply and document D25 relied upon by the respondent, who had credibly explained that the reported lower initial impurities in the tablets prepared according to the patent resulted from the coated core structure rather than the choice of the used excipients.

VIII. Following the appellants' announcement in their letter of 20 July 2021 that they would not take part in the oral proceedings scheduled for 17 September 2021, the oral proceedings were cancelled with the Board's communication of 27 July 2021.

IX. The arguments of the appellants relevant to the present decision can be summerized as follows:

(a) Document D1 already described bilayer pharmaceutical tablet formulations comprising a telmisartan layer including a basic agent such as sodium hydroxide and a HCT layer. The disclosure in document D1 was not limited to bilayered tablets having two contiguous (side-by-side) layers and therefore anticipated the subject-matter of claim 1.

Example 5 of D7 described a process in which telmisartan granules are mixed with a powder blend containing HCT followed by compression of the mixture to form tablets. In the resulting tablet formulation the HCT comprising blend completely surrounded and thus coated the telmisartan granules. Example 5 of document D7 thereby anticipated the subject-matter of claim 12.

(b) Document D1 represented the closest prior art. In as far as the feature of a coating layer around a telmisartan unit were considered to represent a difference between the claimed subject-matter and the tablets described in document D1, no particular effect had been shown to result from this difference. In particular, taking account of the results presented in document D31 the available evidence did not allow for any conclusion that the compositions in accordance with the claims of the patent contained a lower level of initial impurities, had improved stability or provided concomitant dissolution of the active agents. Any observable differences in impurities or stability could not be associated with the coated core structure as the choice of excipients influenced the degradation of the active agents. The

dissolution of the active agents also depended essentially on the used excipients.

As solution to the problem of providing an alternative pharmaceutical form for telmisartan and HCT the claimed subject-matter would be obvious to the skilled person. The co-formulation of incompatible components in pharmaceutical compositions by keeping these components separate in a core and a surrounding coating had been described in documents D23 and D24, which were textbooks in the field of formulation technology. Moreover, document D4 specifically mentioned in the context of combination products comprising a selective l_1 imidazoline receptor agonist, an angiotensin II receptor blocker (ARB) such as telmisartan and optionally a diuretic, in particular HCT, that when two active agents react with one another in a tablet formulation they may be separated from one another in concentric or other coat-type layers, coated beads or granules.

X. The arguments of the respondents relevant to the present decision can be summerized as follows:

(a) Claim 1 of the patent as granted defined a telmisartan containing first unit on which a coating comprising HCT was applied. This definition did not cover tablets of a bilayer structure as defined in document D1.

Claim 12 of the patent as granted defined a process in which a coating comprising HCT is applied to a first unit comprising telmisartan, which is optionally coated with a separating layer. Example

5 of document D7 did not involve the application of a coating.

(b) Document D1 represented the closest prior art. The separation on the basis of a coated core structure in accordance with the claims of the patent surprisingly allowed

- the reduction of total impurities directly following preparation of the coated cores in comparison to compressed bilayer tablets and satisfactory subsequent stability, as demonstrated by the experimental results presented in the patent and the reply to the appeal,

- reduced environmental exposure of the basic telmisartan unit, and

- satisfactory concomitant dissolution of the active agents in spite of the presence of the coating as evidenced by document D25.

The discrepancies in the levels of total impurities and dissolution rates reported in the patent, the reply and document D25 on the one hand and document D31 on the other hand were explained by the likely non-inclusion of telmisartan degradation products in the total impurities according to document D31 and differences in the applied wet granulation step for producing the tablets. The problem to be solved was to be seen in the provision of an improved pharmaceutical formulation for telmisartan and HCT which better addresses the instability of HCT in a basic environment, while at the same time still

providing adequate dissolution of both active compounds, telmisartan and HCT.

The prior art provided no suggestion towards the subject-matter of the claims of the patent as solution to this problem.

XI. The appellants (opponents) requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The respondent (patent proprietor) requested that the appeal be dismissed or subsidiarily that the patent be maintained on the basis of one of its auxiliary requests 1-3 filed before the opposition division with the submission of 19 April 2016.

Reasons for the Decision

1. Admission of document D35

In its communication pursuant to Article 15(1) RPBA (see section 2.2) the Board expressed its preliminary opinion that document D35 was to be admitted into the appeal proceedings. No substantive arguments were submitted by the appellant in response to the Board's communication. Accordingly, the Board has decided to admit document D35 into the appeal proceedings.

2. Novelty

2.1 The claims as granted define the feature of a coating comprising HCT which is applied on a unit comprising telmisartan. The Board agrees with the finding in the

decision under appeal (see sections 3.1-3.2) that the definition of this coating implies that a unit containing telmisartan is provided with a **surrounding layer** containing HCT.

2.2 Document D1 describes a bilayer tablet in which telmisartan and HCT are kept separate in the different layers (see page 5 second paragraph and claim 1) and in which the telmisartan layer contains basic agents (see page 6 paragraph 4 and example 4 on page 17).

The appellants' argument, that the disclosure in document D1 was not limited to bilayered tablets having two contiguous (side-by-side) layers and therefore anticipated claim 1, is not considered convincing. Document D1 does not specifically disclose a relevant unit containing telmisartan which is provided with a **surrounding** layer containing HCT and only discloses embodiments of compressed tablets with contiguous (side-by-side) layers.

2.3 Document D7 describes in example 5 (see paragraph [0087]) a process in which telmisartan granules are mixed with a powder blend comprising HCT with subsequent compression of the mixture to form a tablet.

The appellants' argument, that the preparation of tablets as described in example 5 of document D7 anticipated claim 12, is not considered convincing. The telmisartan granules of the tablet resulting from the process of document D7 may be considered embedded in a matrix containing HCT, but such embedded granules cannot be qualified as units provided with a surrounding **layer** containing HCT.

2.4 The Board therefore concludes that documents D1 and D7 do not anticipate the claims of the patent as granted and that the claimed subject-matter thus meets the requirement of novelty.

3. Inventive step

3.1 The identification of document D1 as closest prior art was not in dispute.

As explained in section 2 above the Board takes the view that the claimed subject-matter differs from this prior art in the feature that the HCT is contained in a coating around a telmisartan unit instead of in a bilayer tablet with separate contiguous telmisartan and HCT layers.

3.2 The patent presents in paragraph [0024] experimental results indicating lower levels of total initial impurities in coated-core tablets prepared in accordance with the patent in comparison to bilayer tablets prepared according to document D1 (see examples 1, 3 and 4 in relation to comparative example 5). Moreover, the results reported in the reply to the appeal (see page 16) indicate satisfactory subsequent stability for tablets prepared in accordance with the patent. Furthermore, the experimental results reported in document D25 indicate that tablets prepared in accordance with the patent (example 3 in the patent, identified as sample 1 in D25) showed in comparison to bilayer tablets prepared according to document D1 (comparative example 5 in the patent, identified as sample 2 in D25) satisfactory concomitant dissolution of the active agents in spite of the coated-core structure (see D25, figures 1-2 and tables 1-2).

In its communication pursuant to Article 15(1) RPBA (see sections 4.3 to 4.8) the Board expressed its preliminary opinion that the respondent had plausibly argued, *inter alia* by reference to document D35, why the diverging data in document D31 did not compromise the conclusions to be drawn from the results presented in the patent, the reply to the appeal and document D25. Moreover, according to the Board's preliminary opinion the respondent had credibly explained that the reported lower initial impurities in the tablets prepared according the patent resulted from the coated-core structure and were not due to the choice of the used excipients (see section 4.7). No substantive arguments were submitted by the appellants in response to the Board's communication. Accordingly, the Board finds no reason to depart from its preliminary opinion.

The Board therefore considers that the technical problem to be solved underlying the subject-matter defined in the claims of the patent as granted may be seen in the provision of improved pharmaceutical formulations in terms of initial impurities without necessarily affecting telmisartan dissolution.

3.3 The Board recognizes no suggestion in the available prior art that would direct the skilled person towards the coated core structure defined in the claims of the patent as granted as solution to the identified technical problem. In this context the Board observes that the appellant contested upon appeal that the claimed subject-matter provided unexpected advantages and argued that the claimed subject-matter was obvious as mere alternative with respect to the formulations of document D1. However, the appellant did not provide reasons why the claimed subject-matter should be considered obvious in case it was considered to

represent a solution to the problem of providing improved formulations.

The subject-matter defined in the claims of the patent as granted was therefore not obvious to the skilled person having regard to the prior art. Accordingly, the Board confirms the finding in the decision under appeal that the patent meets the requirement of inventive step.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated