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Datasheet for the decision of 13 January 2015

Case Number: T 2406/10 - 3.3.01

Application Number: 02780143.0

Publication Number: 1441713

IPC: A61K31/18, A61K9/20, A61K9/28, A61K9/48, A61P13/08

Language of the proceedings: EN

Title of invention:
MODIFIED RELEASE TAMSULOSIN TABLETS

Patent Proprietor:
Synthon B.V.

Opponents:
ETHYPHARM
Teva Pharmaceutical Industries Ltd. et al.
KRKA, tovarna zdravil, d.d., Novo mesto

Headword:
Tamsulosin/SYNTHON

Relevant legal provisions:
EPC Art. 88(2), 54(3)
EPC 1973 Art. 56, 54(4), 100(a)

Keyword:
Novelty - main request (no) -
as the priority is not valid, the examples disclosed both in the priority document and in the prior art under Article 54(3) EPC deprive the subject-matter of the claims of novelty
Inventive step - auxiliary request (yes)

Decisions cited:
G 0002/98, G 0001/92, T 1443/05

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 2406/10 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 January 2015

Appellant: (Patent Proprietor)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma PO Box 18558 2502 EN The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 August 2010 concerning maintenance of the European Patent No. 1441713 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	C. M. Radke
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 441 713 relates to a pharmaceutical modified release tablet containing the (R)-isomer of tamsulosin or a pharmaceutically acceptable salt thereof.

II. The three oppositions filed against the grant of this patent were directed against the patent as a whole and were based on grounds under Article 100(a) EPC (alleged lack of novelty and inventive step) and, as far as opponent 2 is concerned, additionally on grounds under Article 100(b) and (c) EPC. The oppositions were withdrawn on 14 August 2009 (opponent 2), 5 May 2010 (opponent 3) and 11 May 2010 (opponent 1).

III. The documents cited during the opposition proceedings include the following:

(D1) US-A-4 772 475
(D7) E. Galla et al., Pharmaceutical Research, vol. 15, no.5 (1998), 698-705
(D8) J. B. Dressman and C. Reppas, European Journal of Pharmaceutical Sciences II Suppl. 2 (2000), S73-S80
(D10) Priority document US 60/331,055 for the patent in suit
(D15) WO-A-03/039 530
(D18) I. Takayanagi et al., Japan. J. Pharmacol., vol. 42 (1986), 579-582
(D23) Rote Liste 2000, ECV Editio Cantor Verlag, Aulendorf/DE, 82 161 - 82 172
(D25) E. J. van Hoogdalem et al., Journal of Pharmaceutical Sciences, vol. 86, no. 10 (October 1997), 1156-1160

IV. The appeal of the patent proprietor is directed against the interlocutory decision of the opposition division posted on 2 August 2010, that the patent amended according to auxiliary request III submitted during the oral proceedings meets the requirements of the EPC.

In particular, the opposition division decided that
- claims 1 and 29 of the **main request** do not enjoy the priority (D10) claimed, so that document (D15) is novelty-destroying for the subject-matter of these claims;
- the expression "reduced food effect" rendered unclear the claims of **auxiliary request I** then on file; and
- the subject-matter of the claims of **auxiliary request II** then on file was not inventive over document (D23) as the closest prior art if taken in combination with document (D7) or (D8).

V. The present claims are
- claims 1 to 28 of the main request and
- claims 1 to 37 of auxiliary request I,

both filed during the oral proceedings of 13 January 2015.

a) The independent claim of the main request reads as follows:

"1. A pharmaceutical tablet comprising a tablet matrix having dispersed therein 0.1 to 10 mg of (R)-enantiomer of tamsulosin or a pharmaceutically acceptable salt thereof, and optionally having an enteric coating over said matrix, wherein said tablet is a modified release tablet and has a dissolution profile such that in each of the media SIF, FaSSIF, and FeSSIF, said tablet releases not

more than 60% of said tamsulosin at 2 hours elapsed time in USP 2 apparatus using 500 ml of said media at 50-100 rpm paddle speed."

b) The independent claims of auxiliary request I read as follows (the board has indicated (in bold) the features added to each independent claim of auxiliary request I as compared with the corresponding claims of the main request):

"1. **Use of tamsulosin in the manufacture of a** pharmaceutical tablet comprising a tablet matrix having dispersed therein 0.1 to 10 mg of **tamsulosin which is** (R)-enantiomer of tamsulosin or a pharmaceutically acceptable salt thereof, and optionally having an enteric coating over said matrix, wherein said tablet is a modified release tablet and has a dissolution profile such that in each of the media SIF, FaSSIF, and FeSSIF, said tablet releases not more than 60% of said tamsulosin at 2 hours elapsed time in USP 2 apparatus using 500 ml of said media at 50-100 rpm paddle speed, **for treating or ameliorating the conditions of benign prostatic hyperplasia, wherein the tablet is taken under fasted conditions**".

"29. **Use of tamsulosin in the manufacture of a** monolithic pharmaceutical tablet comprising 0.1 to 10mg of **tamsulosin which is** (R)-enantiomer of tamsulosin or a pharmaceutically acceptable salt thereof, 10 wt%-90 wt% hydroxypropyl methylcellulose, and a total tablet weight of 10 to 300 mg, **for treating or ameliorating the conditions of benign prostatic hyperplasia, wherein the tablet is taken under fasted**

conditions".

VI. The board sent a communication on 5 August 2014 in which it argued why it deemed
- the priority claimed in the patent in suit not to be valid and
- the subject-matter of the claims as granted not to be novel in view of document (D15).

VII. The appellant's arguments, as far as relevant for this decision, may be summarised as follows:

Main Request / Novelty

Document (D15) forms part of the state of the art only to the extent that the priority of the patent in suit is not valid. Document (D15) discloses the manufacture of the products of examples 1 to 4 of the patent in suit. However, this does not play a role as the patent in suit enjoys the claimed priority for these examples. The decision T 1443/05 cited in the board's communication is in conflict with the rule that a species can destroy novelty of a genus.

Even if the priority was deemed not to be valid for these examples, they are not relevant as to novelty, as document (D15) does not disclose the dissolution profiles defined in the present claims. The dissolution profiles are not intrinsic properties but are revealed only in contact with the three media. According to decision G 1/92, such extrinsic properties are beyond the teaching of the prior art and thus are not disclosed by disclosing the product as such.

Hence, the examples disclosed in document (D15) are not relevant as to novelty.

Auxiliary Request I / Inventive Step

If document (D1) is considered as the closest prior art, then the subject-matter of the present claims differs from that disclosed in (D1) by the mode of oral administration and by the fact that they require the tamsulosin to be the (R)-enantiomer, whereas (D1) uses the racemate.

The problem posed and solved was to provide an improved or alternative mode of administration.

Documents (D23) and (D25) recommend to administer tamsulosin orally in a capsule in the fed state, namely after a meal. Tamsulosin is highly water-soluble. To achieve the dissolution profiles defined in present claim 1, its release has to be extended. Extended release tablets of tamsulosin exhibit a considerable food effect, i.e. the dissolution of the drug taken in the fed state differs from that taken in the fasted state. Hence, taking the tablet while the stomach is empty may result in an increased peak concentration of the drug. The tablets according to the present claims minimise the food effect so that the patient is free to take it in a fastened state as well.

VIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or, alternatively, of auxiliary request I, both filed during the oral proceedings of 13 January 2015.

IX. The chairman announced the decision of the board at the end of the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Applicable version of the EPC for the provisions on priority, novelty and inventive step

The mention of the grant of the patent in suit was published on 8 August 2007, i.e. before the revised EPC entered into force.

In this case, the transitional provisions state that Articles 54(3) and 88 in the revised version of the EPC and Articles 54(4), 56 and 158 in the version in force before that time are applicable (see Article 1, sections 1 and 3, of the decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000 as published in Special edition No. 1/2007 of the OJ EPO, page 197; see also Article 7 of the transitional provisions published on page 196 of the same publication).

This means that
- Articles 88 and 54(3) EPC are to be applied in the versions of 2007 (in the following denoted as EPC), and
- Articles 54(4), 56 and 158 EPC are to be applied in the versions of 1973 (in the following denoted as EPC 1973).

3. Main request

3.1 It was disputed whether or not the subject-matter of the claims was novel in view of document (D15).

The patent in suit and document (D15) claim the same priority, namely that of the application (D10) filed on 7 November 2001.

Document (D15) has an earlier filing date (1 November 2002) than the patent in suit (6 November 2002). Therefore, the PCT application (D15) could be considered to form part of the state of the art under Article 54(3) EPC

- to the extent that the claims of the patent in suit do not enjoy the priority of document (D10),
- if document (D15) is to be regarded as a European patent application (see Article 158 EPC 1973) and
- to the extent that the requirements under Article 54(4) EPC 1973 are met.

3.2 Priority claimed in the patent in suit

3.2.1 It was not disputed that there is no direct and unambiguous disclosure of any of the release profiles defined in present claims 1-8 of the main request in the priority document (D10)(see (D10), page 12, lines 10-16, and page 13, lines 6-12).

Hence, the subject-matter of independent claim 1 has no basis in the priority document (D10). Likewise, the remaining claims which are directly or indirectly dependent on claim 1 do not enjoy the priority claimed.

3.2.2 The appellant did, however, argue that examples 1 to 4 of the patent in suit enjoyed the priority claimed to the extent that they are disclosed in the priority document (D10).

Hence, it is to be decided whether the claims of the main request enjoy a partial priority with respect to these examples.

According to Article 88(2) EPC "multiple priorities may be claimed for any one claim". This implies that a claim may enjoy a partial priority of an earlier application. The jurisprudence of the boards of appeal acknowledges a partial priority to a claim only if it relates to one or more alternatives within the claim (see G 02/98, OJ EPO 10/2001, 413, points 6.5 to 6.7 of the reasons).

The last sentence under point 6.7 of the reasons of this decision reads as follows:

"The use of a generic term or formula in a claim for which multiple priorities are claimed in accordance with Article 88(2) EPC, second sentence, EPC is perfectly acceptable under Articles 87(1) and 88(3) EPC, provided that it gives rise to the claiming of a limited number of clearly defined alternative subject-matters."

Present claim 1 requires "that in each of the media SIF, FaSSIF, and FeSSIF, said tablet releases not more than 60% of said tamsulosin at 2 hours elapsed time in USP 2 apparatus using 500 ml of said media at 50-100 rpm paddle speed."

Thus, the claim defines a dissolution range of "not more than 60 % ... at 2 hours" for each of the three media. The attribution of a partial priority to parts of the claimed subject-matter would require the identification of a limited number of clearly defined alternatives within the subject-matter claimed. In the

present case, such alternatives could however only pertain to subranges of the dissolution range in each of the three media. A product of a working example within the scope of present claim 1 will however exhibit a dissolution profile corresponding to one distinct value in each of the three media. This combination of three values is just one of an **unlimited** number of combinations within the dissolution ranges for the three media defining the dissolution profile in present claim 1.

Therefore, the product of such a working example cannot be considered as attributable to a **limited** number of clearly defined alternative subject-matters. Consequently, such a product does not meet the requirements laid down in decision G 02/98 for acknowledging a partial priority.

The appellant disagreed with decision T 1443/05 of 4 July 2008, which was cited in the board's communication; the sentence in point 4.2.6 of the reasons contested by the appellant (see point VII above) reads as follows: "Im generischen Wortlaut des Anspruchs 1 kann keine eindeutige Alternative bestimmt werden, die die Beispiele umfasst, und die das Prioritätsrecht hätte begründen können (siehe Punkt 4.1.9 oben und G 2/98 ibid, Punkt 6.7)." That means that in decision T 1443/05, no unambiguous alternative could be determined in claim 1 which encompassed the examples and could have formed the basis for a priority right. This is perfectly in line with the passage of G 2/98 cited above. This sentence explains why the working examples in this case did not enjoy a partial priority. The reason given, i.e. a lack of a distinguishable alternative within the subject-matter of claim 1 to which the examples could have been

attributed, is not related to the question of novelty or analogous to a novelty test. The assessment is whether subject-matter which is directly and unambiguously disclosed in the priority document by way of an abstract definition of features can be related to a limited number of alternatives which share these features and which can be distinguished within the subject-matter of the claim for which the benefit from the effect of the priority right is sought. Hence, contrary to the appellant's arguments, T 1443/05 is not in contradiction with the principle that a species destroys the novelty of the genus comprising said species.

For this reason, the board does not share the view of the appellant that the working examples of the patent in suit enjoy the priority of document (D10) to the extent that they are disclosed in said priority document.

3.2.3 The consequence of the conclusions drawn under points 3.2.1 and 3.2.2 above is that none of the claims of the main request enjoys the priority of document (D10), be it partially or in its entirety.

3.3 The PCT application (D15) was published in English. It entered into the European phase with effect from 28 May 2004, and the respective fees were paid by debit order on the same date, including designation fees for all the 24 contracting states which were members of the EPO at that time. That any remaining requirements under Article 158 EPC 1973 were met is evident from the fact that a respective patent was granted (EP-B-1 443 917). Hence, (D15) is to be regarded as a European patent application.

Therefore, the whole content of document (D15) as filed forms part of the state of the art under Article 54(3) EPC for the patent in suit, insofar as, according to Article 54(4) EPC 1973, "a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published", in the present case for all the 24 contracting states designated in the patent in suit. The whole content of document (D15) includes its working examples. This is in line with decision T 1443/05 cited above, in particular with points 4.2.3, 4.2.4 and 4.2.6 of the reasons.

3.4 Document (D15) discloses on page 21, line 1, to page 22, line 2, the manufacture of the product of batch G of example 3, parts a)-c) of the patent in suit.

The patent in suit shows on page 9, lines 44-51, and in Figure 2 that the product of batch G of example 3, part c) has the dissolution profiles required in claim 1 of the main request.

3.4.1 The appellant argued that the products being claimed differed from the ones disclosed in document (D15) because (D15) does not disclose the dissolution profiles defined in the present claims. It considered these profiles to be extrinsic features which are not disclosed by disclosing the product as such (see the second paragraph of point VII above).

3.4.2 Claim 1 of the main request requires "a dissolution profile such that in each of the media SIF, FaSSIF, and FeSSIF, said tablet releases not more than 60% of said tamsulosin at 2 hours elapsed time in USP 2 apparatus using 500 ml of said media at 50-100 rpm paddle speed." (see under Va) above).

According to the patent in suit,

- "SIF represents a standard intestinal condition. FeSSIF is tailored to better represent the fed state while FaSSIF is tailored to better represent the fasting state" (see page 4, lines 32-33), and
- the "media serve to model *in vitro* the intestinal conditions encountered *in vivo*" (see page 3, lines 1-3).

3.4.3 The appellant based its arguments that document (D15) did not explicitly disclose these dissolution profiles on decision G 01/92 (OJ EPO 1993, 277). In point 3 of the reasons it is stated that "a commercially available product per se does not implicitly disclose anything beyond its composition or internal structure. Extrinsic characteristics, which are only revealed when the product is exposed to interaction with specifically chosen outside conditions, e.g., reactants or the like, in order to provide a particular effect or result or to discover potential results or capabilities, therefore point beyond the product per se as they are dependent on deliberate choices being made. Typical examples are the application as a pharmaceutical product of a known substance or composition (cf. Article 54(5) EPC) and the use of a known compound for a particular purpose, based on a new technical effect (cf. G 2/88, OJ EPO 1990, 93). Thus, such characteristics cannot be considered as already having been made available to the public."

3.4.4 In order to assess whether or not the dissolution profiles defined in present claim 1 are extrinsic properties within the meaning of decision G 01/92, a closer look at the disclosure of document (D15) may be helpful.

Document (D15) relates to an oral dosage form of tamsulosin, in particular to a slow release tablet (see page 12, lines 3-7). It is preferred that the tablets have a certain release profile in phosphate buffer of pH 6.8, *inter alia* 40-75 % release in 2 hours (see page 12, lines 8-16).

"For therapeutic purposes, bioabsorption of tamsulosin in body fluids should preferably proceed in the small intestines" (page 12, lines 17-18).

In summary, document (D15) is focused on a tablet which slowly releases tamsulosin into the small intestines. As an *in vitro test* for this requirement, a certain dissolution profile is suggested.

3.4.5 As evident from point 3.4.2 above, the three media to be used according to present claim 1 likewise are to simulate the conditions present in the intestines. Furthermore "bioabsorption of tamsulosin in body fluids should preferably proceed in the **small** intestines" (page 6, lines 9-11, of the patent in suit; emphasis added by the board).

Therefore, the dissolution media required according to present claim 1 are just means to simulate how the tablet disclosed in document (D15) is dissolved in the small intestines, namely at the site disclosed in (D15) and in a way disclosed there, namely slowly.

Hence, the dissolution profiles defined in present claim 1 cannot be considered to be extrinsic properties within the meaning of decision G 01/92. Moreover, the media in which these profiles are to be determined were known prior to the filing date of the patent in suit

(see document (D7), page 699, right-hand column, under the heading "*Composition of Various Media*", and Table II on page 700; note that the SIF_{sp} disclosed there is "without pancreatin" like the SIF used in the patent in suit (see page 3, line 56, of the patent)).

3.5 As a consequence of this, the fact that
- document (D15) discloses the product of batch G of example 3, part c) of the patent in suit;
- the patent in suit shows on page 9, lines 44-51, and in Figure 2 that the product of batch G of example 3, part c) has the dissolution profiles required in claim 1 of the main request, and
- these dissolution profiles are intrinsic properties of said product which can be analysed and reproduced by the skilled person (cf. G 1/92, Conclusion, point 1)

leads to the conclusion that the subject-matter of claim 1 of the main request lacks novelty under Article 54(3) EPC for all the contracting states designated in the patent in suit.

3.6 The board can only decide on a request as a whole. Therefore, the main request was refused.

4. Auxiliary request I

4.1 Novelty

The subject-matter of the independent claims of auxiliary request I differs from the disclosure of document (D15) in that they require that tamsulosin is the (R)-enantiomer and in that the tablet is taken under fasted conditions. No other of the cited documents are relevant as to novelty.

Therefore, the subject-matter of the claims of the auxiliary request I is novel.

4.2 Inventive step

4.2.1 Closest prior art

Document (D15) belongs to the prior art under Article 54(3) EPC and is not to be considered when assessing inventive step (see Article 56 EPC 1973).

Document (D1) may be regarded as the closest prior art.

It claims a pharmaceutical controlled-release formulation in which the physiologically active substance is "(5-[2-[2-(o-ethoxyphenoxy)ethylamino]-propyl}-2-methoxybenzenesulfonamide hydrochloride (YM-12617)" (see claim 4), namely tamsulosin hydrochloride (see paragraph [0002] of the patent in suit). According to column 4, lines 28-30, "YM-12617 shows an α-blocking action and can be used for the treatment of ..., lower urinary disease". The formulation may be in the form of a tablet (see, e.g. example 20 and the respective dissolution rates indicated in Table 1 in column 5).

YM-12617 is a racemate (see document (D18), page 579, left-hand column, line 8 below the abstract).

Document (D1) discloses neither the use of a tamsulosin which is the (R)-enantiomer nor the administration under fasted conditions.

4.2.2 The problem posed was to provide an alternative mode of administration.

4.2.3 As a solution to this problem, the patent in suit suggests to use a modified release tablet of the (R)-enantiomer under fasted conditions, where the tablet has the release profiles specified in claim 1 or the composition according to claim 29. The examples of the patent in suit show that this problem is solved.

As stated in paragraph [0004] of the patent in suit, the commercialised modified release capsule containing tamsulosin "suffers from a drawback in that it exhibits a food effect. A food effect refers to the difference in bioabsorption or bioavailability of a drug arising from administration to a fasting patient (an empty stomach) versus a fed patient (food in the stomach)". Taking the capsule after a meal provides "a flatter and more controlled release blood plasma profile in comparison to administering under fasting conditions, albeit with a loss in bioavailability". Vice versa, taking the commercialised capsule under fasted condition provides a steeper release profile which may give rise to the undesirable side effects mentioned in paragraph [0007] of the patent in suit. This may be the reason why document (D23) recommends to take the OMNIC® capsule after the first meal of the day (see the entry 82 171 "**Dos.:** 1 Retardkps. morgens nach dem Frühstück od. nach der ersten Mahlzeit des Tages"). Hence, it was not immediately obvious to take a modified release formulation of tamsulosin under fasted conditions.

It is evident that the administration of such a modified release formulation also under fasted conditions made sense only if the food effect was minimised.

Present claim 1 requires that the tablet releases not more than 60% of tamsulosin at 2 hours in simulated

intestinal fluid (SIF), fed state simulated intestinal fluid (FeSSIF), as well as in fasted state simulated intestinal fluid (FaSSIF). This requirement leads to a flattening of the dissolution curves in the three media and, consequently, may decrease the food effect. This is illustrated in Figures 1 and 2 on page 19 of the patent in suit, where Figure 1 refers to the commercial product and Figure 2 to the uncoated tablet according to batch G of example 3 according to the present claims. Such a flattening of the dissolution curves may, e.g., be achieved by selecting a proper polymeric matrix (see paragraph [0023] of the patent in suit). A comparison of Figure 5 (batch H, coated, 35% by weight of hydroxypropylmethylcellulose (HPMC)) with the curves for the coated batch N in Figure 6 (20% by weight of HPMC) shows that the curves for the dissolution profiles are the flatter the more HPMC is used.

None of the prior art documents suggests that such measures permit the administration of modified release tamsulosin tablets under fasted conditions.

For these reasons, the subject-matter of claims 1 and 29 of the auxiliary request is based on an inventive step. The same applies

- to claims 2 to 28 which are dependent from claim 1 and
- to claims 30-37, which are dependent from claim 29.

4.2.4 For these reasons, the subject-matter of the claims of the auxiliary request is based on an inventive step.

4.3 The board is not aware of any deficiency of the claims of the auxiliary request which could prejudice the maintenance of the patent on their basis.

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 maintain the patent with the following claims and a description to be adapted thereto:

   Claims no. 1 to 37 of auxiliary request I filed during the oral proceedings of 13 January 2015.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated