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**Datasheet for the decision
of 23 September 2014**

Case Number: T 0926/10 - 3.3.07

Application Number: 99919614.0

Publication Number: 1121103

IPC: A61K9/50, A61K9/20, A61K31/44

Language of the proceedings: EN

Title of invention:
ORALLY DISINTEGRABLE TABLETS COMPRISING A BENZIMIDAZOLE

Patent Proprietor:
Takeda Pharmaceutical Company Limited

Opponent:
Hexal AG

Headword:

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:
Inventive step - main request (no)
Inventive step - auxiliary request 1 (no)
Late-filed auxiliary requests 2 to 5 - admitted (no)

Decisions cited:
T 1685/07

Catchword:



**Beschwerdekammern
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Chambres de recours**

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Case Number: T 0926/10 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 23 September 2014

Appellant: Hexal AG
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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
2 March 2010 concerning maintenance of the
European Patent No. 1121103 in amended form.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
D. T. Keeling

Summary of Facts and Submissions

I. The appeal of the opponent (appellant) lies against the decision of the opposition division to maintain European patent No. 1121103 in amended form.

II. The patent had been opposed under Articles 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, the invention was not sufficiently disclosed, and the subject-matter of the patent extended beyond the content of the application as filed. The documents filed during opposition proceedings included the following:

D1: WO 96/01623

D2: Drugs made in Germany, 37, 2, 1994

D4: US 5,178,878

E1: Chem. Pharm. Bull., 51(8), 942-947, 2003

III. The decision of the opposition division was based on the set of claims filed with letter of 23 June 2008 as auxiliary request 1. This set of claims represented the highest ranking request pending before the first instance at the end of the oral proceedings.

Claim 1 of this request read as follows:

"1. An orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400µm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of a benzimidazole compound or a salt thereof and (ii) an additive comprising a water-soluble sugar alcohol, wherein the enteric coating layer comprises an aqueous

enteric polymer agent and further comprises a sustained release agent."

IV. The decision of the opposition division can be summarized as follows:

- a) The subject-matter of auxiliary request 1 complied with Article 123(2) and (3) EPC. The requirements of sufficiency of disclosure and novelty were also met.

- b) The tablets of claim 1 differed from the tablets disclosed in the closest prior art document D1 on account of the presence of a water-soluble sugar alcohol and a sustained release agent in the enteric coating. The water-soluble sugar alcohol had the function of providing sufficient strength to the tablets and of promoting the oral disintegration. These effects were shown in the examples. The technical problem was formulated as the provision of "oral disintegrable tablets comprising a benzimidazole derivative having sufficient strength and which disintegrate orally". Document D1 neither suggested the oral disintegration of the tablets disclosed therein nor provided any motivation for preparing orally disintegrable tablets containing a benzimidazole drug. Thus, the skilled person would have had no reason for combining the teaching of D1 with the teaching of document D4. Moreover, the combined teaching of D1 with the other prior art documents would not have led to the tablets defined in claim 1. The subject-matter of the claims was therefore inventive over the prior art.

- V. The appellant lodged an appeal against that decision. In the statement setting out the grounds of appeal it limited its arguments to the requirements of sufficiency of disclosure and inventive step.
- VI. The patent proprietor (respondent) replied to the statement setting out the grounds of appeal with a letter sent on 18 November 2010.
- VII. On 11 August 2014 the respondent filed six sets of claims as main request and auxiliary requests 1 to 5. The claims of the main request were identical to the claims of the request allowed by the opposition division.

Claim 1 of auxiliary request 1 differed from claim 1 of the main request in the addition of the following feature at the end of the claim:

"...and wherein the oral disintegration time is one minute or less."

Claim 1 of auxiliary requests 2 to 5 was based on claim 1 of auxiliary request 1 with the addition of the following limitations:

- a) auxiliary request 2: the presence of a foaming agent in the additive was excluded by means of a disclaimer
- b) auxiliary request 3: the benzimidazole compound was restricted to lansoprazole
- c) auxiliary request 4: the amount of sustained-release agent was defined as being from 5 to 15% weight relative to 100% weight of the enteric polymer agent

- d) auxiliary request 5: the composition coated by an enteric coating layer was further coated by an additional layer comprising a water-soluble sugar alcohol.

VIII. Oral proceedings were held before the board on 23 September 2014.

IX. As far as relevant for the present decision, the appellant's arguments can be summarised as follows:

Main request - Inventive Step

Document D1 represented the closest prior art for the assessment of inventive step. This document disclosed tablets dispersible in an aqueous liquid, comprising units coated by an enteric layer and containing omeprazole as active ingredient. Although D1 did not disclose orally disintegrable tablets, these were covered by the general teaching of this document. Moreover, it was clear that at least the formulations prepared in examples 13, 16 and 17 were suitable as orally disintegrable tablets in view of the presence of the disintegrant crospovidone.

The size of the core material of the tablets of document D1 was between 100 and 4000 μm . Hence, the particle diameter of 400 μm or less specified in claim 1 of the patent, did not represent a distinguishing feature.

The claimed tablets differed from those disclosed in document D1 mainly in the presence of a sugar alcohol and of a sustained release agent. The technical problem was to be seen in the provision of an alternative

tablet formulation of enterically coated granules containing a benzimidazole compound.

Sugar alcohols were commonly used as binders. For instance, sorbitol and mannitol were used as binding agents respectively in D2 and D4. As to the sustained release agent, there were no effects associated to the use of this substance. The impact on the acid-resistance after compression, was to be disregarded for the assessment of inventive step because this effect was disclosed only in the post-published document E1. The patent was silent as to any possible impact of the sustained release agent on the acid resistance after compression. This effect was in any case not surprising because document D2 suggested that a coating comprising a mixture of sustained release agent and enteric polymer agent was more resistant to compression forces than a coating containing only an enteric polymer. As to the results disclosed in reference example III of D1, which showed that an omeprazole-containing tablet having the same coating system suggested by the authors of D2 had a low acid resistance, these represented an isolated experiment and therefore they were not sufficient to establish a prejudice against the combined use of sustained release agent and enteric polymer agent in the coating layer.

Auxiliary request 1 - Inventive Step

The subject-matter of this request was substantially identical to the subject-matter of the main request in that the indication of the disintegration time had simply the effect of clarifying the meaning of the expression "orally disintegrable". This request was therefore not inventive for the same reasons given for the main request.

Admissibility of auxiliary requests 2 to 5

The limiting features introduced in claim 1 of auxiliary requests 2 to 5 were independent from each other, thereby defining different inventions. Some requests created a new case for the assessment of inventive step. These requests were therefore not to be admitted into the proceedings.

- X. As far as relevant for the present decision, the respondent's arguments can be summarised as follows:

Main request - Inventive Step

D1 was the closest prior art. This document did not disclose orally disintegrable tablets and the appellant did not submit any evidence to show that the tablets prepared in some examples were orally disintegrable in view of the presence of a disintegrating agent. Furthermore, the hardness of the tablets disclosed in D1 suggested that these tablets were not orally disintegrable.

The presence of a sustained release agent in the coating layer, represented a further distinguishing feature over the tablets disclosed in D1. The effect of this agent was to decrease the cleavage and crushing of the enteric layer. Although this effect was not disclosed in the patent, it was to be considered in the formulation of the technical problem because it was supported by the data disclosed in document E1 and it related to a problem generally known in the art. Furthermore, various examples of the patent contained data that demonstrated the good acid resistance of the tablets.

None of the examples of D1 disclosed tablets containing a water-soluble sugar alcohol as tablet excipient. Hence, the presence of a water-soluble sugar alcohol as an additive represented a further distinguishing feature of the tablets claimed in the patent.

The coated pellets of the most relevant example of document D1, i.e. example 17, appeared to have a particle diameter greater than 400 μm . Accordingly, the tablets of the opposed patent differed from those of document D1 also in the size of the granules.

The technical problem solved by the invention was the provision of an alternative tablet formulation of enterically coated granules containing a benzimidazole compound which exhibited satisfactory strength and acid resistance.

The results of reference example III of D1 would have discouraged the skilled person from following the teaching of D2 as to the composition of the coating layer. Moreover, D2 did not relate to orally disintegrable tablets.

D4 disclosed an effervescent oral dosage form which disintegrated in the mouth by releasing microparticles. Example 1 of this document related to tablets containing mannitol as binding agent. However, the active ingredient of the tablet of this example was incorporated in a matrix-type microparticle instead of being included in coated granules as the tablets of the opposed patent or the tablets of D1. Accordingly, the skilled person would have not modified the composition of the tablets of D1 in the light of the teaching of D4. Furthermore, D4 was not concerned with the problem of delivering intact enteric-coated granules into the

intestine. Hence, the skilled person confronted with the problem of providing a formulation for an acid-sensitive active ingredient, would have not considered this document.

Auxiliary request 1 - Inventive Step

The subject-matter of the first auxiliary request was characterised by an additional distinguishing feature over the disclosure of D1, namely the dissolution time. Thus, the arguments developed in respect to the main request applied also to the first auxiliary request.

Admissibility of auxiliary requests 2 to 5.

With the exception of auxiliary request 2, the auxiliary requests related to combination of granted claims. Hence, the limitations introduced in these claims could not be regarded as unforeseeable.

- XI. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

- XII. The respondent requested as main request that the appeal be dismissed or, in the alternative, that the patent be maintained on the basis of the claims of one of the five auxiliary requests, all filed by letter of 11 August 2014.

Reasons for the Decision

Main request

- 1. *Inventive step*

- 1.1 The invention addresses the problem of providing a solid oral formulation for an acid-labile active substance which is a benzimidazole compound.

Closest prior art

- 1.2 The board concurs with the parties and with the opposition division that document D1 represents the closest prior art. This document discloses a pharmaceutical preparation in the form of a tablet which comprises multiple units coated by an enteric layer. The active ingredient included in said units is omeprazole, i.e. a benzimidazole compound.
- 1.2.1 As pointed out by the opposition division in its decision, the tablets defined in claim 1 of the patent differ from the tablets disclosed in D1 in the presence of a water-soluble sugar alcohol as an additive and in the presence of a sustained release agent in the coating. Furthermore, although it is stated on page 6 of D1 that the tablets can be dispersed in an aqueous liquid, there is no clear indication in the document that the tablets are orally disintegrable. Hence, this characteristic represents a further distinguishing feature of the tablet of the patent over the tablets of D1. As to the size of granules, the board agrees with the appellant that this does not represent a distinguishing feature since the size of the units of the tablets of D1 is preferably between 100 and 2000 μm (page 8) and therefore largely overlaps with the range of 400 μm or less specified in claim 1 of the patent.

Technical problem

- 1.3 The parties substantially agreed in regarding the technical problem in the light of D1 as the provision

of an alternative tablet formulation of enterically coated granules containing a benzimidazole compound. There was however no agreement as to whether the definition should also include an indication that the tablets exhibit a satisfactory acid resistance, as required by the respondent. In the appellant's opinion this effect was to be disregarded in that it emerged only from the post-published document E1.

1.3.1 Having regard to this issue, it is observed that the patent provides data concerning the "remaining ratio" or the "acid resistance" in respect to the tablets of examples 4 to 6, 8 and 9. As explained by the respondent during the oral proceedings, these parameters provide a measure of the capacity of the enteric coating layer to withstand the compression during the tableting process. The data for the examples mentioned above indicate that the coating layer is not substantially damaged by the compression forces. In addition to that, document E1 shows that the presence in the coating layer of ethyl acrylate-methyl metacrylate copolymer (trade name: Eudragit NE30D®, page 942), i.e. a sustained release agent, enhances the acid resistance.

1.3.2 The board notes that little information is given in the patent as to the general issues concerning the stability of the coating layer during the tableting procedure, and nothing is said with regard to the effect of the sustained release agent on the acid resistance. This effect finds an experimental support only in the post-published document E1. Nevertheless, it appears justified in the present case to take account of said effect in the formulation of the technical problem. As indicated above, the patent discloses the value of the acid resistance for some

exemplified tablets. Even though no explanation is given for the results obtained, the board considers that a skilled person would obviously deduce that the resistance of the coating layer to the compression forces is in relation with the properties of the layer itself and therefore also of its composition. In this respect it is also noted that from D1 (page 4, lines 1-6) and D2 (paragraph 2.2.3.1), it is clear that the skilled person was well-aware before the priority date of the various problems arising from the compression of coated granules. Accordingly, despite the absence of any clear indication in the patent, in the board's opinion an expert in this technical area would be able to infer that the sustained release agent which is a component of the layer has an impact on the acid resistance. The data of document E1 can therefore be considered as a confirmation of the deductions that a skilled person would make on the basis of the information given in the patent and of his knowledge of the technical field.

- 1.3.3 The patent discloses also the disintegration times for the tablets prepared in examples 2 to 9. The values (between 20 and 35 seconds) indicate that the tablets disintegrate rapidly in the mouth upon administration.
- 1.3.4 In the light of the above, the technical problem solved by the subject-matter of claim 1 is defined as the provision of an alternative tablet formulation of enterically coated granules containing a benzimidazole compound which exhibits satisfactory acid resistance.

Obviousness of the solution

- 1.4 The first question to be answered is whether the skilled person faced with the problem of providing

alternative tablets to those disclosed in the closest prior art, would consider the preparation of orally disintegrable tablets. In this respect the board agrees with the appellant that the general teaching of D1 covers also orally disintegrable tablets. Indeed, in the general description of the invention provided on page 5 (lines 18 to 28) or in claim 1, the tablets are characterised only in respect to the units that they contain. There are no restrictions as to the dissolution profile of the tablets, their mode of administration or their excipients. The main feature of the tablets of D1 is represented by the enterically coated layered pellets contained therein, which must protect the acid-sensitive omeprazole. Apart from the fact of containing these pellets, there are no other requirements that the tablets of D1 need to satisfy. Hence, although not explicitly mentioned, the compression into orally disintegrable tablets is one of the possible ways of processing the omeprazole-containing pellets of D1. In the absence of any established prejudice against the preparation of orally disintegrable tablets for benzimidazole compounds, there is no inventive contribution in the mere selection of this particular kind of formulation.

1.5 As indicated in 1.2.1 above, the tablets defined in claim 1 of the patent differ from the tablets disclosed in D1 also in the presence of a water-soluble sugar alcohol as an additive and in the presence of a sustained release agent in the coating.

1.5.1 As to the water-soluble sugar alcohol, the respondent explained that the function of this additive was to act as binding agent and to affect the oral disintegration of the tablet.

Sugar alcohols are commonly used as tablets excipients. For instance, document D2 discloses the use of sorbitol as excipient in fast disintegrating tablets containing coated particles (see Formulation 4 of table 3 and paragraphs 2.2.2 to 2.2.4). Furthermore, in example I of document D4, mannitol is used in the compression of microparticles to form effervescent tablets. As stated also by the respondent, in this case mannitol acts possibly as binder. The respondent pointed out also that the microparticles of example I of D4 are quite different from the granules of the claimed tablets especially on account of the absence of a coating layer. However the fact that sorbitol is used for the preparation of the tablets of D2 which contain granules having various types of coatings, suggests that the use of a sugar alcohol as tablet's excipient is not limited to specific formulations. The board is therefore unable to recognise any possible inventive contribution in the use of a sugar-alcohol as additive of pharmaceutical tablets if its function is basically to act as binder.

Concerning any possible effect of the water-soluble sugar alcohol on the oral disintegration, it is noted that all the tablets exemplified in the patent contain crospovidone or low-substituted hydroxypropyl cellulose or a mixture of them as an additive. These substances are known as disintegrant agents (see [0097]). The board concurs with the opinion expressed by the appellant that the rapid disintegration of the tablets in the mouth is to be attributed mainly to the presence of said disintegrants rather than the action of the sugar alcohol. No evidence has been submitted by the respondent to show that in the absence of the disintegrants the tablets would still disintegrate in less than one minute. Even admitting a possible contribution of the sugar-alcohol to the disintegration

process determined by the disintegrant, this effect would not be surprising in the light of the fact that the sugar must be soluble in water.

1.5.2 With regard to the presence of a sustained release agent in the coating layer, the most relevant teaching is provided by document D2. In paragraph 2.2.3.1 of this document ("Tabletting of enteric-coating ASA particles", page 57), it is explained that the enteric polymer agent Eudragit L30D-55®, when used to coat pellets containing acetylsalicylic acid as active ingredient, it "forms very brittle films which cannot withstand the compression forces". The result is the formation of cracks on the surface of the coated particles, from which the active ingredient is released immediately in the stomach. However, when the coating contains a mixture of Eudragit L30D-55® and Eudragit NE30D® no formation of crack occurs. The coating film in this case is more flexible and resistant to gastric fluids (see also paragraph bridging pages 59 and 60). Eudragit NE30D® is the same sustained release polymer used in all the examples of the opposed patent and also in the formulation of the post-published document E1 (see table 3). Accordingly, document D2 provides a clear teaching that the acid resistance of an enteric coating layer can be improved by the addition of Eudragit NE30D®, which is a sustained release agent.

1.5.3 The respondent argued that the poor acid resistance of the tablet prepared in reference example III of D1, would have discouraged the skilled person from following the teaching of D2 as to the composition of the coating layer.

Reference example III of D1 relates to the preparation of a tablet containing pellets coated with the same

coating system used in the formulation n°9 of D2, i.e a mixture of Eudragit L30D-55® and Eudragit NE30D®. The acid resistance of this tablet is 82%. The board agrees with the opinion expressed by the appellant that the result of a single test would not necessarily induce the skilled person to disregard the teaching of D2 as to the positive effects of Eudragit NE30D®. His attitude would possibly be to verify whether certain parameters of formulation 9 of D2 need to be modified or optimised, in order to observe the same beneficial effects observed by the authors of D2. Independently from this consideration, it is noted that document D1 discloses also the acid resistance for two other reference examples relating to tablets containing omeprazole pellets (reference example I) or lansoprazole pellets (reference example II). In both cases the pellets are coated by an enteric layer and no mention is made as to the presence of a sustained release agent in the coating. The acid resistance of these tablets is respectively 6% and 25%, i.e. much lower than the acid resistance measured for the tablet of reference example III. Thus, taken together the results of the acid resistance of the tablets of the reference examples of D1 appear to support the general teaching of D2 as to the beneficial effects of the sustained release agent Eudragit NE30D® in the coating layer.

- 1.5.4 The further argument of the respondent, that the skilled person would not consider the teaching of D2 since this document does not relate to orally disintegrable tablets, is also not convincing. There is no evidence that the problem of providing granules coated by an enteric layer which can withstand the compression during the tableting process, is somehow in relation with the oral disintegration profile of the

tablet. The fact that both D1 and D2 address the problem of the resistance of the enteric coating layer, although no mention is made in these documents of orally disintegrable tablets, demonstrates that said problem occurs when granules having an enteric coating layer are compressed into a tablet, regardless of the disintegration profile of the latter.

It follows from the above, that the addition of a sustained release agent in the coating layer in order to safeguard its resistance during the compression, is suggested by D2.

- 1.6 In the light of the above reasons, the board concludes that the subject-matter of the main request does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. *Inventive step*

- 2.1 The subject-matter of claim 1 of this request differs from the subject-matter of claim 1 of the main request only in the indication that the disintegration time is of one minute or less. This additional characterisation of the tablets does not result in any substantial change in comparison with the situation of the main request since the expression "orally disintegrable tablets", interpreted in the context of the claimed invention, already implies a short disintegration time (see paragraph [0105]). Hence, the observations made in respect to the main request apply also to the subject-matter of auxiliary request 1.
- 2.2 It follows that the subject-matter of auxiliary request 1 does not meet the requirements of Article 56 EPC.

Auxiliary requests 2 to 5

3. *Admissibility*

3.1 The auxiliary requests were submitted on 11 August 2014, i.e. when oral proceedings had already been arranged. The admissibility of these requests is therefore at the board's discretion (Articles 13(1) and 13(3) of the Rules of Procedure of the Board of Appeal (RPBA), Supplementary publication to OJ EPO 1/2014, 44).

3.2 Claim 1 of auxiliary requests 2 to 5 contains the same limitation introduced in claim 1 of auxiliary request 1 with regard to the disintegration time of the tablet. In addition, each request includes a further limiting feature. These additional limiting features differ from each other and concern also different structural characteristics of the tablet. In greater detail:

- (a) The additional feature of auxiliary request 2 concerns the definition of the additive.
- (b) The additional feature of auxiliary request 3 concerns the definition of the active ingredient
- (c) The additional feature of auxiliary request 4 concerns the definition of the enteric coating layer
- (d) The additional feature of auxiliary request 5 concerns the presence of an additional coating layer.

It can be seen from the above, that the subject-matters of auxiliary requests 2 to 5 rather than converging towards a single preferred aspect of the invention, are diverging in independent alternatives. This is a

relevant factor in the assessment of the admissibility of late filed requests (see for instance T 1685/07, point 6.5 of the reasons). By filing these requests the respondent is therefore developing various lines of defence with no apparent relation. This is effectively requiring the appellant and the board to examine a new set of more or less unrelated inventions, which is contrary to the principle of procedural economy.

The respondent has argued that most of the features introduced in auxiliary requests 2 to 5 were already present in the granted claims. This argument, however, does not affect the validity of the observations made above because the common features of auxiliary requests 2 to 5 are the features already present in auxiliary request 1. Since this request does not comply with the requirements of Article 56 EPC, the appellant and the board would be obliged to carry out an independent examination for each request, in order to assess whether the additional feature may have an impact on the inventiveness of the subject-matter of the claim.

- 3.3 In view of this, the board considers it appropriate to exercise its discretion under Article 13 RPBA by not admitting auxiliary requests 2 to 5 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 Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated