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Datasheet for the decision of 19 April 2012

Case Number: T 0234/08 - 3.3.02

Application Number: 98921690.8

Publication Number: 989848

IPC: A61K 9/28

Language of the proceedings: EN

Title of invention:
Film-coated tablet for improved upper gastrointestinal tract safety

Patentee:
Warner Chilcott Company, LLC

Opponents:
Hexal AG
F.Hoffmann-La Roche AG

Headword:
Film-coated tablet for stomach delivery

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
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Keyword:
"Admission of late-filed documents into the proceedings (no)"
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0234/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 19 April 2012

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 27 November 2007 revoking European patent No. 989848 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: D. Boulois
R. Cramer

Summary of Facts and Submissions

I. European patent No. 0 989 848, based on application No. 98 921 690.8, was granted on the basis of a set of 9 claims. Independent claim 1 read as follows:

"1. A novel oral dosage form to be delivered to the stomach, said dosage form comprising a safe and effective amount of an active ingredient selected from the group consisting of tetracycline antibiotics, iron preparations, quinidine, nonsteroidal anti-inflammatory drugs, alprenolol, ascorbic acid, captopril, theophylline, zidovoudine, bisphosphonates or mixtures thereof and pharmaceutically-acceptable excipients, wherein said oral dosage form is characterized by being generally oval form and film coated to facilitate rapid esophageal transit and avoid irritation in the mouth, buccal cavity, pharynx, and esophagus, and comprising dimensions of from 0.58 to 2.16 cm (0.23 to 0.85 inches) for length, from 0.28 to 1.02 cm (0.11 to 0.4 inches) for width and from 0.19 to 0.76 cm (0.075 to 0.3 inches) for thickness."

II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, as well as for exclusion from patentability on the ground of Article 52(2) EPC, and under Article 100(b) EPC for insufficiency of disclosure.

III. The documents cited during the opposition and appeal proceedings included the following:

(18) K.S. Channer et al., Journal of Pharmacy and Pharmacology, 1985, 37, pp 126-129

(20) WO93/09785

(21) "Pharmazeutika Bestimmungsliste", 1996/1997, 9. Ausgabe, pp 8-63.

IV. By its decision pronounced at the oral proceedings on 17 October 2007, the opposition division revoked the patent under Article 102(1)(3) EPC 1973, on the grounds that none of the requests met the requirements of the EPC.

In said decision the opposition division decided that the requirements of Article 83 EPC were met.
The main request was found not to meet the requirements of Article 54 EPC.
The first auxiliary request was found to be not inventive over document (20). Claim 1 differed from the teaching of document (20) by the nature of the coating and the claimed dimensions.
According to the opposition division, the patent in suit did not show any unexpected effect related to the specific dimensions, which could not represent a distinguishing feature for the assessment of inventive step. The underlying problem in view of document (20) could be seen in the provision of a pharmaceutical formulation for releasing the active agent at an alternative site, whereby irritations caused by oesophageal reflux represented an acceptable disadvantage.
Document (20) disclosed that drug release in the mouth, pharynx or oesophagus should be avoided. Document (18) disclosed that film coating enhanced oesophageal transit. Thus, the opposition division found that the replacement of an enteric coating by a different film-coating was a matter of routine for the skilled person,

when the disadvantage of oesophageal reflux was accepted.

Claim 1 of auxiliary requests 2 and 3 lacked inventive step over document (20) for the same reasons.

V. The patentee (appellant) lodged an appeal against that decision.

VI. With the grounds of appeal, the appellant filed a new main request and auxiliary request 1, as well as arguments regarding sufficiency, novelty and inventive step. The independent claims read as follows:

(a) main request:

"1. A novel oral dosage form to be delivered to the stomach, said dosage form comprising a safe and effective amount of risedronate and pharmaceutically-acceptable excipients, wherein said oral dosage form is characterized by being generally oval form and film coated with a film coating which is soluble at pH from 1.2 to 5 to facilitate rapid esophageal transit and avoid irritation in the mouth, buccal cavity, pharynx, and esophagus, and comprising dimensions of from 0.58 to 2.16 cm (0.23 to 0.85 inches) for length, from 0.28 to 1.02 cm (0.11 to 0.4 inches) for width and from 0.19 to 0.76 cm (0.075 to 0.3 inches) for thickness."

(b) auxiliary request 1:

"1. A novel oral dosage form to be delivered to the stomach, said dosage form comprising a safe and effective amount of risedronate sodium and pharmaceutically-acceptable excipients, wherein said oral dosage form is characterized by being generally

oval form and film coated with a film coating which is soluble at pH from 1.2 to 5 to facilitate rapid esophageal transit and avoid irritation in the mouth, buccal cavity, pharynx, and esophagus, and comprising dimensions of from 0.58 to 2.16 cm (0.23 to 0.85 inches) for length, from 0.28 to 1.02 cm (0.11 to 0.4 inches) for width and from 0.19 to 0.76 cm (0.075 to 0.3 inches) for thickness."

VII. The opponent-respondents 01 and 02 filed arguments against the inventive step of the main and auxiliary requests with letters dated respectively 14 August 2008 and 18 August 2008.
The appellant commented on the replies to the grounds of appeal with its letter of 13 September 2011.
Further counter-arguments were filed by respondent 01 with its letter dated 12 March 2012.

VIII. With a letter dated 10 April 2012, the appellant filed new evidence in the form of the experimental reports named "Exhibit I", "Exhibit II" and "Exhibit III".

IX. Oral proceedings took place on 19 April 2012.

X. The appellant's arguments can be summarised as follows:

As regards the admission of Exhibits I-III into the proceedings, the documents were very pertinent for inventive step and should therefore be admitted into the appeal proceedings. Their high relevance to the proceedings should take precedence, since the proceedings could be conducted more efficiently with this evidence.

They were filed as an immediate response to a letter of the respondent dated 12 March 2012. A copy was provided to the respondents, who should have had enough time to study them, all the more since the documents are neither complex in nature, nor cumbersome and time-consuming.

As regards inventive step, document (20) should be considered as the closest prior art. The problem in this document was the same as in the contested patent, but the solution, namely to deliver the active ingredient in the upper intestine and not in the stomach, was different. The objective problem over this document was the provision of an effective delivery of risedronate to successfully treat diseases while minimising or avoiding undesirable release.
A skilled person would consult document (20) for a solution. The solution foreseen in document (20) was to prevent release in the stomach. The oral dosage forms of document (20) were not designed to deliver the active ingredient in the stomach. Nor was there any incentive in document (20) to modify this solution.

XI. The respondents' arguments can be summarised as follows:

As regards the admission of "Exhibits I-III" into the proceedings, according to respondent 01 all documents filed after the filing of the grounds of appeal were late-filed and should not be admitted. Moreover, the said experimental reports "Exhibits I-III" were not relevant for the object of appeal.
The point regarding a potential improvement of bioavailability had already been raised in the letter

dated 14 August 2008, and the latest letter dated 12 March 2012 was only a repetition.
Furthermore, the exhibits did not give a comparison of bioavailability between a film-coated tablet and an enteric-coated tablet, and were therefore irrelevant.
In addition, the contested patent did not mention the problem of bioavailability.

As regards inventive step, document (20) was seen as the closest prior art by respondent 01, since this document shared the same problem as the contested patent.
The solution in the contested patent was a solid dosage form allowing a rapid oesophagial transit, while in document (20) it was a delayed release of the active ingredient through an enteric coating. In the contested patent, the rapid release was achieved by the oval shape, the specific dimensions and the film coating.
In document (20) the solution was to be found in example 3, which showed an oval-shaped tablet.
The difference between claim 1 of the patent and document (20) was the use of another coating and the absence of any indication regarding the dimensions of the tablet.
According to the respondent 01, the subjective problem was the provision of an alternative dosage form protecting the mucosa of the mouth and the oesophagus from irritation and ulceration.
The patent however did not show anywhere that this problem had been solved, nor that a tablet as claimed provided a rapid oesophagal transit.
The problem had to be reformulated as the provision of a further dosage form of risedronate.

The tablets of example 3 of document (20) had a weight of 300 mg. Document (21) showed pictures of tablets of such a weight on pages 50 and 51, which showed that the tablets of example 3 should have the claimed dimensions.
Furthermore, document (18) incited the skilled person to use oval-shaped and film-coated tablets to provide a rapid oesophagial transit.
The subject-matter of claim 1 of the main request was therefore obvious.
As regards the inventive step of auxiliary request 1, document (20) disclosed in example 3 the same salt of risedronate, which meant that the subject-matter of claim 1 of the auxiliary request was not inventive over document (20).

As regards the admission of "Exhibits I-III" into the proceedings, according to respondent 02 the objection raised by the opponents about bioavailability was not recent, and the exhibits did not address any new objection.
As regards inventive step, respondent 02 was of the opinion that document (20) was be the closest prior art. The tablets in document (20) differed in their enteric coating and the absence of definition of the dimensions. There was no specific effect linked with the dimensions, so the only relevant distinguishing feature was the nature of the coating.
In view of document (20) the underlying technical problem could be seen as the provision of a pharmaceutical composition comprising risedronate for releasing the active ingredient at an alternative site.
The replacement of an enteric coating by a different film coating had long been known and was routine for

the skilled person. Therefore the subject-matter of claim 1 of the main request was not inventive in view of document (20).
As regards the inventive step of the auxiliary request, there was no effect linked with the use of the sodium salt of risedronate, and claim 1 of the auxiliary request was also not inventive.

XII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main or auxiliary requests filed with the grounds of appeal.

XIII. Both respondents (opponents 1 and 2) requested that the appeal be dismissed.

Reasons for the decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 *Admission of Exhibits I-III into the proceedings*

1.2.1 Under Article 13(1) RPBA, admission of changes to a party's submission after the filing of the statement of grounds of appeal and the reply thereto is at the board's discretion and depends upon the circumstances of the case under consideration.

The experimental reports "Exhibit I", "Exhibit II" and "Exhibit III" were submitted by the appellant with a

letter dated 10 April 2012, and therefore at a very late stage in the proceedings.

1.2.2 It was clear from the beginning of the appeal proceedings that the assessment of inventive step would be a main issue in the present case. The existence of a technical effect in the form of an improvement of bioavailability of the claimed tablet was presented by the appellant in its grounds of appeal as an important argument in favour of inventive step.
The absence of substantiation of this assertion, and in particular the lack of evidence in the form of experimental tests, was raised initially by respondent 01 in its reply to the grounds of appeal dated 14 August 2008, and last repeated in its further letter dated 12 March 2012.
The submission of the experimental reports "Exhibit I", "Exhibit II" and "Exhibit III" with a letter dated 10 April 2012 cannot therefore be considered as a reply to a recent objection or observation from the respondents. Consequently, there are no valid reasons for their late filing.

Moreover, the data were submitted to demonstrate that a film-coated tablet of the present invention has an unexpected improved bioavailability vis-à-vis an enteric-coated tablet as disclosed in document (20), and therefore to show the presence of inventive step in the present invention vis-à-vis said document (20). However, none of the submitted experimental results give a direct comparison between a film-coated tablet and an enteric-coated tablet. The documents are *prima facie* irrelevant for this reason.

1.2.3 The appellant argues that there is an obligation to consider evidence of general interest and that this obligation should take precedence in the proceedings. It also asserts that the proceedings can be conducted more pragmatically with the said evidence, namely the experimental reports "Exhibit I", "Exhibit II" and "Exhibit III", supporting its reasoning. Nor it adds, is the evidence complex, or its analysis difficult or time-consuming.

The board however cannot follow these arguments.
Exhibit I shows a comparison of the bioavailability of risedronate from a single dose administered directly in the stomach, in the second part of the duodenum or in the terminal ileum. Exhibit II compares the bioavailability of risedronate from gelatine capsules *vs*. enteric-coated tablets, and from gelatine capsules *vs*. film-coated tablets. Exhibit III is a study of the relative bioavailability of risedronate in relation to food and time, and from a gelatine capsule as compared with from an enteric-coated tablet.
Some of the submitted tests, in particular Exhibit I or part of Exhibit III, do not appear to be *prima facie* of general interest for the discussion on inventive step. Moreover, none of the submitted experimental tests allows a direct comparison between a film-coated tablet and an enteric-coated tablet. Rather, the tests provide an indirect comparison through a common comparison of a film-coated tablet and an enteric-coated tablet with a capsule form. Drawing a conclusion from such an indirect comparison cannot be seen as clear and simple.

Finally, it is questionable whether an improvement of bioavailability could have been taken into account for

the discussion on inventive step, as this problem or any related point is absent from the application as originally filed.

1.2.4 Accordingly, the experimental reports "Exhibit I", "Exhibit II" and "Exhibit III" are not admitted into the proceedings.

2. *Main request - inventive step*

The present invention relates to the provision of a dosage form comprising risedronate that protects the epithelial and mucosal tissue of the mouth, the buccal cavity, the pharynx, the larynx and the oesophagus (see par. [0001], [0006], [0007] of the contested patent). The oval-shaped film-coated dosage form facilitates a rapid oesophageal transit time and thereby avoids the release of risedronate until it reaches the stomach.

2.1 Document (20) is concerned with the protection of the epithelial and mucosal tissues of the mouth, the buccal cavity, the pharynx, the larynx and the oesophagus from erosion or ulceration (see page 1 lines 5-18), and constitutes the closest prior art.
The compositions used in document (20) are enteric-coated dosage forms which release the active agent, in particular risedronate, to the lower intestinal tract of a human or animal, prohibiting its release in the buccal cavity, the pharynx, oesophagus, stomach and anterior duodenum (see page 4, lines 10-13, page 5, lines 1-2, page 7, lines 11-22, page 9, lines 9-12, page 11, lines 23-30). An enteric-coated oval-shaped tablet comprising risedronate and having a weight compatible with the dimensions claimed in claim 1 of

the contested patent is disclosed in at least one example of document (20) (see example 3).
As an alternative to an enteric coating, document (20) suggests using a pH-independent sustained-release coating comprising cellulose derivatives (see page 12, lines 23-32; page 15, line 7; page 20, lines 20-26; claim 8). These polymers are similar to the cellulose derivatives used in the contested patent as components of the film-coating soluble at a pH from 1.2 to 5.

2.2 The contested patent comprises two examples of oval-shaped tablets comprising risedronate coated with a cellulose derivative. The examples are silent regarding the final size of the tablets.
While it was an essential point of the contested patent (see for instance its par. [0009], [0010], [0030]), none of the said examples provides any experimental results in the form of *in vivo* or *in vitro* tests showing that the claimed dosage forms do indeed allow a rapid oesophageal transit and a delivery of risedronate in the stomach.
As a consequence, none of the examples in the contested patent is suitable for demonstrating a beneficial effect over the prior art.
In the absence of any experimental evidence or arguments establishing a minimum plausibility for the presence of an improvement vis-à-vis the closest state of the art, the problem underlying the present invention can only be seen as the provision of a further dosage form of risedronate.
The solution is a dosage form of risedronate in oval form, film coated with a film coating which is soluble at pH from 1.2 to 5, and having the specific claimed dimensions.

In view of the information found in the description of the contested patent, the board is convinced that the above problem has been plausibly solved.

2.3 Thus the question to be answered is whether the proposed solution would have been obvious to the person skilled in the art.
Document (20) suggests the alternative use of cellulose derivatives such as ethylcellulose, hydroxypropylmethyl cellulose or carboxymethyl cellulose as a pH independent coating. The skilled person therefore has an incentive in document (20) to replace the enteric polymers with a film-coating polymer as claimed in the contested patent.

The subject-matter of claim 1 of the main request is not inventive over document (20). The requirements of Article 56 EPC are therefore not met.

3. *Auxiliary request 1:*

Claim 1 of auxiliary request 1 differs from claim 1 of the main request by the restriction to the sodium salt of risedronate.
As the same active ingredient is disclosed in document (20), the reasoning applied to claim 1 of the main request applies *mutatis mutandis* to claim 1 of auxiliary request I. The requirements of Article 56 EPC are therefore not met.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald