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**Datasheet for the decision
of 11 June 2015**

Case Number: T 0177/13 - 3.3.07

Application Number: 05735411.0

Publication Number: 1753395

IPC: A61K9/20, A61K9/32

Language of the proceedings: EN

Title of invention:

ENTERIC SOLID ORAL DOSAGE FORM OF A BISPHOSPHONATE CONTAINING
A CHELATING AGENT

Patent Proprietor:

Warner Chilcott Company, LLC

Opponent:

APOTEX INC.

Headword:

ENTERIC SOLID ORAL DOSAGE FORM OF A BISPHOSPHONATE CONTAINING
A CHELATING AGENT/Warner Chilcott Company, LLC

Relevant legal provisions:

RPBA Art. 13
EPC R. 80
EPC Art. 56

Keyword:

Late filed requests not admitted into the proceedings -
Main request, auxiliary request 3
Late filed requests admitted into the proceedings -
Auxiliary requests 1, 1A
Inventive step - Auxiliary requests 1, 1A, 2 (no)
Inventive step - technical prejudice in the art (no)
Inventive step - Obvious multiple selections

Decisions cited:

G 0002/08

Catchword:



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Case Number: T 0177/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 June 2015

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 19 November
2012 revoking European patent No. 1753395
pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
P. Schmitz

Summary of Facts and Submissions

- I. European patent No. 1 753 395 based on application No. 05 735 411.0 was granted on the basis of a set of 9 claims.

Independent claim 1 as granted read as follows:

"1. An oral dosage form of a pharmaceutical composition comprising:

a) a bisphosphonate selected from risedronate, and salts, esters, hydrates, hemihydrates, polymorphs and solvates thereof, and combinations thereof,

b) from 75 mg to 250 mg of disodium EDTA; and

c) an enteric coating which provides for release of the the bisphosphonate and the EDTA in the lower gastrointestinal tract of a mammal;

wherein the molar ratio of the disodium EDTA to the biphosphonate is at least 2:1."

- II. An opposition was filed under Article 100 (a) and (b) EPC on the grounds that its subject-matter lacked novelty and inventive step and the patent was not sufficiently disclosed.

- III. The documents cited during the opposition and appeal proceedings included the following:
(O1): BR 0 106 601 (English translation)
(O3): WO 93/09785 A1
(O11): Burgio, D.E., "Declaration under 37 C.F.R., §§ 1.68 and 1.132"

- IV. The appeal by the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on 4 sets of claims, namely a main request corresponding to the claims as

granted and auxiliary requests 1-3 filed during the oral proceedings held on 18 October 2012.

According to the decision under appeal, document (O1) was considered to be the closest prior art, although this choice was contested by the patentee, whose main argument was that this document was not enabling and was dedicated to another problem.

The subject-matter of claim 1 of the main request differed from document (O1) in that the molar ratio of chelating agent to risedronate used in the formulation is higher, namely at least 2:1 in claim 1 instead of higher than 50% mol/mol in document (O1).

The opposition division could not see a comparison between the teaching of document (O1) and the claimed invention in example XIX of the contested patent, or in document (O11). Hence, the objective technical problem was seen as being the provision of an alternative dosage form comprising risedronate, sodium EDTA and an enteric coating.

The opposition division could also not see that document (O1) provided a technical prejudice against increasing quantities of chelating agents with regard to risedronate and saw the optimization of the ratio of chelate to risedronate as part of a routine procedure. Claim 1 of the main request did not meet the requirements of inventive step for these reasons.

The subject-matter of claim 1 of auxiliary request 1 differed from claim 1 of the main request in that the enteric coating was further defined by the feature "*which does not dissolve in gastrointestinal fluids at a pH below 5.5, and does dissolve in gastrointestinal fluids at a pH 5.5 or above*". Since the scope of claim 1 of auxiliary request 1 was considered to be the same as for the main request, the subject-matter of claim 1

of auxiliary request 1 also did not meet the requirements of inventive step.

The subject-matter of claim 1 of auxiliary request 2 differed from claim 1 of the main request in that the enteric coating was defined by the feature "*initiates release of the bisphosphonate and the ETA primarily in the duodenum and/or jejunum*". According to the opposition division, there was no effect linked with this feature, and no advantage could be seen in the release of risedronate in the specified duodenum or jejunum. Hence, the technical problem was seen as the provision of an alternative dosage form comprising risedronate, sodium EDTA and an enteric coating, which achieves a similar bioavailability of risedronate in the jejunum and ileum with or without food. Since document (O1) suggested the initial portion of the small intestines as particularly important for a good absorption of risedronate and since there was no effect shown resulting from the distinguishing feature, the skilled person would have considered the solution of claim 1 obvious.

The subject-matter of claim 1 of auxiliary request 3 differed from claim 1 of the main request in that the enteric coating was defined by the feature "*which is made from poly(methacrylic acid, ethyl acrylate) 1:1*". The distinguishing features between claim 1 of auxiliary request 3 and document (O1) were the molar ratio of disodium EDTA to risedronate and the specific enteric coating claimed. No effect linked with the first difference was identified and the effect of the further distinguishing feature was the achievement of a similar bioavailability of risedronate in the jejunum and ileum with or in absence of food. No technical effect was thus associated with the specific enteric

coating. The technical problem was seen as the provision of an alternative oral dosage form comprising risedronate, sodium EDTA and an enteric coating, which achieves a similar bioavailability of risedronate in the jejunum and ileum with or without food. The polymer chosen was a commercially available enteric coating known to release in the small intestine, especially in view of document (O3). It was obvious for the skilled person to choose this coating. Claim 1 of auxiliary request 3 lacked inventive step over document (O1).

- V. The patent proprietor (appellant) filed an appeal against said decision. With the statement of grounds of appeal the appellant filed a main request and six auxiliary requests and submitted new documents (A1)-(A10). The submitted documents included the following:
(A2): Janner, M. et al, "Sodium EDTA enhances Intestinal Absorption of Two Biphosphonates", *Calcif. Tissue Int.*, Vol. 49, pp. 280-283 (1991)
- VI. With a letter dated 15 December 2013, the appellant submitted a further new document.
(A11): Supplemental Declaration
- VII. In a communication dated 6 May 2015 sent in preparation of oral proceedings, the Board gave its preliminary opinion. In particular, it commented on example XIX of the contested patent and the experimental results of document (O11), especially regarding their adequacy to demonstrate a bio-equivalence between an administration in fed and fasted state.
- VIII. With a letter dated 11 May 2015, the respondent submitted a new document:
(O16): Excerpt from NIH article "The digestive System and How it Works".

- IX. With a letter dated 2 June 2015, the respondent submitted new documents:
(017): "Guidance for Industry - Food Effect Bioavailability and Fed Bioequivalence Studies", FDA CDER, December 2002
(018): "Draft Guidance on Risedronate Sodium", FDA, recommended August 2005, revised December 2008
(019): "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", EMA, London, December 14, 2000.
- X. With a letter dated 4 June 2015, the appellant submitted new documents and new auxiliary requests 1-3 replacing the auxiliary requests filed previously. The submitted documents included the following:
(A13): Excerpt from Emergency Motion for an Injunction Pending Appeal submitted to the United States Court of Appeal for the Federal Circuit
- XI. Oral Proceedings took place on 11 June 2015. At the beginning of oral proceedings, the appellant presented a main request, first, second and third auxiliary requests, these being the requests which had already been filed and a new auxiliary request 1A.

The subject-matter of the independent claims 1 of the requests read as follows, the difference(s) compared with the claims as granted shown in bold:

(a) Main request

"1. An oral dosage form of a pharmaceutical composition **for use in treating or preventing diseases characterised by abnormal calcium and phosphate metabolism**, comprising:

a) a bisphosphonate selected from risedronate, and salts, esters, hydrates, hemihydrates, polymorphs and solvates thereof, and combinations thereof,
b) from 75 mg to 250 mg of disodium EDTA; and
c) an enteric coating which provides for release of the bisphosphonate and the EDTA in the lower gastrointestinal tract of a mammal;
wherein the molar ratio of the disodium EDTA to the biphosphonate is at least 2:1

and wherein the use is administration of a weekly oral dosage form containing from 10 to 50 mg risedronate on a risedronate anhydrous monosodium salt basis."

(b) Auxiliary request 1

"1. An oral dosage form of a pharmaceutical composition, **wherein the oral dosage form is a tablet** comprising:

a) ~~a biphosphonate selected from~~ **35 mg risedronate on a risedronate anhydrous monosodium salt basis**, ~~and salts, esters, hydrates, hemihydrates, polymorphs and solvates thereof, and combinations thereof,~~
b) **100 mg** of disodium EDTA; and
c) an enteric coating which provides for release of the the bisphosphonate and the EDTA in the lower gastrointestinal tract of a mammal;
wherein the molar ratio of the disodium EDTA to the biphosphonate is at least 2:1."

(c) Auxiliary request 1A

The subject-matter of claim 1 of this request is identical to claim 1 of auxiliary request 1, this request differing from auxiliary request 1 by the maintenance of dependent claims 2 to 4, which were suppressed in auxiliary request 1.

(d) Auxiliary request 2

The claims of this request are the claims as granted.

(e) Auxiliary request 3

"1. An oral dosage form of a pharmaceutical composition **for use in treating or preventing diseases characterised by abnormal calcium and phosphate metabolism**, comprising:

a) a bisphosphonate selected from risedronate, and salts, esters, hydrates, hemihydrates, polymorphs and solvates thereof, and combinations thereof,

b) from 75 mg to 250 mg of disodium EDTA; and

c) an enteric coating which provides for release of the the bisphosphonate and the EDTA in the lower gastrointestinal tract of a mammal;

wherein the molar ratio of the disodium EDTA to the biphosphonate is at least 2:1

and wherein the use is administration of a daily oral dosage form containing from 1 mg to 10 mg risedronate on a risedronate anhydrous monosodium salt basis; or a weekly oral dosage form containing from 10 to 50 mg risedronate on a risedronate anhydrous monosodium salt basis; or a twice monthly oral dosage form containing from 20 to 100 mg risedronate; or an oral dosage form that is administered three times per month containing from 15 to 75 mg risedronate, preferably about 50 mg risedronate on a risedronate anhydrous monosodium salt basis; or a monthly oral dosage form containing from 50 to 200 mg risedronate on a risedronate anhydrous monosodium salt basis."

XII. The arguments of the appellant may be summarized as follows:

Admission of the requests into the procedure

The requests filed during oral proceedings were already filed with the letter dated 4 June 2015 and they were in reply to points raised in the preliminary opinion of the Board.

Furthermore, they did not change the course of the proceedings. The claims of the main and auxiliary requests 3 were limited to a dosage regime, for which an unexpected effect existed.

Dependent claims were deleted in auxiliary request 1 for reasons of potential lack of support of the features of these claims in combination with the features of claim 1. Auxiliary request 1A was similar to auxiliary request 1 but with the previously deleted dependent claims present again.

Auxiliary request 1, 1A and 2 - Inventive step

The closest prior art was the immediate release form Actonel® disclosed in document (O11) and not document (O1).

Document (O1) did not mention the problem of the food effect, did not present any data showing that EDTA could be used safely in humans and that delayed release forms could be used to solve the problem of food effect of the biphosphonates. The tablets disclosed in document (O1) included preferably alendronate and not risedronate.

Moreover, it was not possible to provide comparative tests over the teaching of document (O1), since it was not possible to provide a comparative example illustrating said teaching. It was indeed necessary to make multiple selections from the teaching of document (O1), among the active agent, the chelating agent, the dose of risedronate and EDTA, the molar ratio between risedronate and EDTA, the particular tablet form, thus in total 6 selections over the disclosure of document (O1).

There was also a technical prejudice to use EDTA in oral dosage forms, and the skilled person would not have incorporated EDTA in such amounts in oral tablets. The excess of EDTA allowed to decrease the interactions between risedronate and the ions present in the intestines, and at the filing date, this amount of EDTA required to increase the absorption of a biphosphonate was found to be clinically unacceptable.

Moreover, the problem of document (O1) was to diminish the dose of the biphosphonate in the dosage form, and was not the same problem as in the contested patent.

The problem was the provision of a dosage which could be given after the breakfast and had the same bioavailability as when taken before breakfast, i.e. the suppression of the food effect.

The suppression of the food effect was shown by studies 107 and 120 of document (O11), which showed that administration of a delayed dosage form of risedronate in fed and fasted state had the same bioavailability.

In any case, the skilled person would not have made a selection among 6 categories of features from the

disclosure of document (O1) to arrive at the claimed subject-matter.

This argumentation was also valid for auxiliary request 2.

XIII. The arguments of the respondent may be summarized as follows

Admission of the requests into the procedure

All the requests were late filed and should not be admitted in the procedure. Some requests included medical use claims, which had never been discussed before the first instance and belonged to a different category of claims. The claims were also not clearly allowable.

Moreover, auxiliary request 1 did not meet the requirements of Rule 80 EPC, since dependent claims had been deleted.

Auxiliary request 1, 1A and 2 - Inventive step

Document (O1) was the closest prior art, and related to oral dosage forms of biphosphonate with a better intestinal absorption. It intended to solve the same problem as the contested patent, namely the low bioavailability of biphosphonate by oral administration (see page 2, 3rd par. and page 4, 1st par.).

As regards the selection claimed in claim 1 of auxiliary request 1, the following was pointed out:

- the problem raised in document (O1) was common to all biphosphonate, including risedronate
- disodium EDTA was disclosed as preferred chelating agent (see document (O1), claims 7-9)

- the dose of disodium EDTA to the biphosphonate was explicitly given as a molar ratio of at least 1:1, with a maximum dose of 175 mg (see pages 6 and 7). Since no beneficial effect had been shown over document (O1), the problem was the provision of an alternative dosage form of risedronate. The solution to this problem was not inventive.

The bioavailability was better when the molar ratio between EDA and risedronate was 1:1, as shown by document (O11). All the selected features of claim 1 of auxiliary request 1 had no effect, and were thus the result of an arbitrary choice.

As to the argument of the appellant that the disclosure of document (O1) was not enabling, there was no basis for it. As regard to the potential existence of a technical prejudice to use EDTA in an oral dosage form, this is contradicted by the teaching of document (O1), which mentions the problem and solves it by the use of an enteric coating (see document (O1), page 3).

The studies disclosed in document O11 showed that the food effect had not been suppressed, and even showed a better result on this point when the molar ratio between EDTA and risedronate was 1:1.

XIV. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and that a patent be maintained on the basis of the main request, or alternatively the first auxiliary request, auxiliary request 1A, the second or the third auxiliary requests, as submitted at the beginning of the oral proceedings.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. Admission of the main request, auxiliary requests 1, 1A and 3 into the proceedings

- 1.1 Main request

The main request corresponds to auxiliary request 2 filed with letter dated 4 June 2015 shortly before the oral proceedings, thus at a late stage in the proceedings.

Claim 1 of the main request has been drafted under the form of a purpose related product claim, i.e. a composition for use in a method under Article 53(c) EPC, where novelty and inventive step is derived from the intended medical use. Said claim is restricted by a feature relating to a dosage regime which needs thus to be taken into account when considering novelty and inventive step (see G 2/08). Such type of claim and specific feature of dosage regime had not been present in any request discussed during the opposition proceedings and was not the subject of the decision of the opposition division. Said type of claim and feature of dosage regime had also not been submitted previously in the appeal proceedings, even though they were present in claim 1 of auxiliary requests 3, 5 and 6 submitted with the statement of grounds of appeal, but not in a claim relating to a composition for use in a method under Article 53(c) EPC, thus not relevant for considering novelty and inventive step.

This request constitutes therefore a fresh case introduced at a very late stage of the proceedings, which raises points that the Board cannot reasonably deal.

The justification given by the appellant that the rewording of the product claims to a product for use claims represents a response to the comments made by the Board in its preliminary opinion cannot be followed, since said preliminary opinion did not relate to requests comprising a claim drafted in the form of claim 1 of the main request and all comments related to the product claims of the requests filed with the statement of ground of appeal.

Moreover, the Board's communication cannot be taken as a justification for submitting new requests that a party could have filed earlier, since it is intended as guidance for the oral proceedings and is not an invitation nor an instruction of the Board to file new submissions (see Case Law of the Boards of Appeal, 7th Edition, 2013, chapter IV.E.4.4.11.). This point was emphasized by point 11 of the Board's communication by the following wording: *"Should a party wish to file further submissions, attention is drawn to Article 13(1) and (3) RPBA. The admission of any amendment to a party's case would have to be considered at the oral proceedings"*.

Thus, the Board considers that it is appropriate to exercise its discretionary power to not admit the main request into the procedure in accordance with Article 13 of the Rules of Procedure of the Boards of Appeal.

1.2 Auxiliary request 1

Auxiliary request 1 corresponds to auxiliary request 3 filed with letter dated 4 June 2015. The subject-matter of its claims differ from the claims as granted by the incorporation of the features of dependent claim 2 into claim 1 and the suppression of dependent claims 3-5. The amendments to this request are of a simple and clear nature and *prima facie* address the issues raised by the decision of the opposition and the respondent's objections without giving rise to new ones and without adding complexity to the case under consideration.

The justification given by the appellant as to the suppression of the dependent claims 3-5 appears to be an anticipation of a possible absence of explicit basis for the combination of the subject-matter of these claims with the subject-matter of claim 1. This suppression is thus occasioned by a possible ground of opposition and meets also Rule 80 EPC.

Therefore, although submitted after the filing of the statement of the grounds of appeal, auxiliary request 1 is admitted into the proceedings (Article 13 RPBA) and meets also the requirements of Rule 80 EPC.

1.3 Auxiliary request 1A

Auxiliary request 1A differs from auxiliary request 1 in the maintenance of dependent claims 3-5 as granted. The argumentation given for auxiliary request 1 applies *mutatis mutandis* for auxiliary request 1A which is admitted into the proceedings (Article 13 RPBA).

1.4 Auxiliary request 3

Auxiliary request 3 differs from the claims as granted in an analogous manner to the way in which the main

request differs from it, namely by a dosage regime (see point 1.1 above).

Consequently, auxiliary request 3 is not admitted into the proceedings for analogous reasons to those stated above for the main request (Article 13 RPBA).

2. Auxiliary request 1 - Inventive step

2.1 The claimed invention relates to oral dosage forms comprising 35 mg of risedronate, 100 mg of disodium EDTA, and an enteric coating. The oral dosage form intends to provide in particular a pharmaceutically effective absorption of risedronate when administered with or without food or beverages (see par. [0001] of the patent). The use of disodium EDTA as absorption enhancer increases the intestinal permeability at high doses, enabling administration of the bisphosphonate active ingredient, namely risedronate with food or beverages. Furthermore, the coated oral dosage forms of the invention provide for delayed release of the bisphosphonate and the chelating agent in the lower gastrointestinal tract, which may alleviate the upper gastrointestinal irritation experienced with other oral bisphosphonate dosage forms and the need to remain upright for thirty minutes post-dose administration (see par. [0009]-[0011]).

2.2 Closest prior art

2.2.1 Document (O1) has been selected by the respondent as closest prior art. This choice was contested by the appellant, who saw in the immediate release dosage form of risedronate disclosed in document (O11) the closest prior art.

The teaching of document (O1) has furthermore been contested on several points by the appellant, namely on the lack of pharmacokinetic, pharmacologic and clinical safety data.

- 2.2.2 The immediate release dosage form as disclosed in document (O11) is the commercially available tablet Actonel® comprising 35 mg of risedronate, without any chelating agent and enteric coating (see page 5, last par.).
- 2.2.3 Document (O1) discloses an oral pharmaceutical composition containing a bisphosphonate and a chelating agent, the composition being enterically coated (see claims 1, 9, 11, 14, 17; page 4, lines 23-30; page 6, lines 18-20). Risedronate is disclosed among a list of bisphosphonates (see page 6, line 1; claim 11) and disodium EDTA is mentioned as the preferred chelating agent (see page 5, lines 1-8; claim 9). The dosage form can be in the form of a tablet (see claim 20). The amount of EDTA in the oral dosage form is said to not exceed 175 mg (see page 6, lines 3-8; claims 7-9), while the amount of bisphosphonate is comprised between 1 and 150 mg for each ingestion, or from 0.01 to 2.15 mg per kg of body weight. The proportion between the chelating agent and the bisphosphonate is preferably higher than 50% mol/mol, which corresponds to a mole ratio of chelating agent to bisphosphonate of higher than 1:1.

Document (O1) further discloses that the use of the enteric coating allows the delivery of EDTA in the intestine, avoiding the conversion into undesirable compounds in the stomach. Once in the intestine, EDTA captures the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain

free for absorption, and increases the permeability of the intestinal mucosa, thereby increasing the capacity to absorb biphosphonate (see page 3, line 1 - page 4, line 9).

Document (01) thus does not disclose directly and unambiguously a tablet comprising risedronate and disodium EDTA in the claimed amounts, since this specific combination constitutes a multiple selection over the teaching of document (01).

- 2.2.4 The Board is of the opinion that document (01) not only is a feasible starting point for assessing inventive step but constitutes indeed the closest state of the art, since this document not only presents a similarity of the technical problem of the claimed invention, but also discloses a combination of features which constitutes the most promising starting point for assessing the obviousness of the claimed invention.

As regard the teaching of document (01), the Board considers that there are no reasons to question the clinical or pharmacological efficiency of the compositions disclosed in document (01), in the absence of concrete and sufficient evidence to unequivocally prove that document (01) is indeed speculative, i.e. not enabling. The disclosure of this document is sufficient to enable a skilled person to practice the teaching, taking into account the general knowledge in the field, and challenging the teaching of this document would also call into question the teaching of the claimed invention.

As regards the absence of pharmacokinetic data in document (01) this cannot imply the absence of enabling disclosure, since pharmacokinetic data are not essential to the teaching of document (01).

- 2.2.5 Moreover, as regards the choice of the closest prior art, the Board reminds that if there are several different prior art documents, each of which might plausibly be taken as a starting point for the assessment of inventive step, it is established case law that inventive step be assessed relative to all these pieces of prior art before any decision confirming inventive step is taken. There is thus not necessarily only "one closest prior art" document. If there are more workable routes, i.e. routes starting from different documents, which may lead to the invention, the rationale of the problem-solution approach requires an examination of the invention in respect of all these workable routes, before inventive step can be acknowledged. Correspondingly, if one of these workable routes shows the invention is obvious, the presence of inventive step is to be denied.
- 2.3 According to the appellant, the problem to be solved is the provision of an oral dosage form permitting an effective absorption of risedronate with or without food or beverage, thus suppressing the food effect.
- 2.4 As a solution to this problem the contested patent proposes the enteric coated oral dosage form of claim 1 of auxiliary request 1 in particular in tablet form and comprising 35 mg of risedronate and 100 mg of disodium EDTA.
- 2.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect.
- 2.5.1 The patent in suit provides 20 examples, example XIX comparing the administration of a combination of 35 mg risedronate and 100 mg disodium EDTA delivered to

different locations in the gastrointestinal tract in fed and fasted state. For fasted administration, subjects fast overnight and the dose is administered in the morning. For fed administration, subjects are fed a light breakfast and at approximately 3 hours later subjects take the study medication. Immediately following the passing of the study medication from the stomach, these subjects eat a breakfast. The ratio of of fed to fasted urine recovery is then measured.

The results of example XIX do however not appear to be relevant for the assessment of the suppression of the food effect, i.e. the bio-equivalence between a fasted and a fed administration. It is indeed unthinkable that an administration 3 hours after a light breakfast might be envisaged as a fed administration, even more as an administration with food or beverage. The delay of 3 hours between the meal and the administration of the medical composition makes it irrelevant for assessing the fed administration of said composition.

The standardized and conventional protocol of fed administration required by regulatory authorities such as the FDA includes indeed an overnight fast of at least 10 hours, and an administration of the dosage form within 30 minutes after ingestion of a test "high fat meal" (see document (O11), page 4, or document (O17) pages 5-6). As none of these standard requirements has been followed in the experiments of example XIX, said experiments do not allow an objective comparison between a fasted and a fed administration of the dosage form, and thus cannot be used to show the suppression of the food effect, i.e. a bio-equivalence between the fed and fasted administration.

2.5.2 Document (O11) has been further submitted by the appellant to demonstrate the existence of the beneficial effect., i.e. the suppression of the food effect and the bio-equivalence between an administration in fasted and fed state.

(a) In this document, the study 120 shows a comparison between an administration in fed and fasted state of a delayed release composition comprising 35 mg of risedronate and 100 mg of disodium EDTA by following the Guidance for Industry given by the FDA. The study gives the measurement of the urinary excretion of risedronate over 72 hours by treatment. The result is a 30% reduction in the urinary excretion between the fasted and fed administration.

This study does however not succeed in showing a bio-equivalence between the administration of the dosage form in fasted and fed state and the suppression of the food effect.

The pharmacokinetic parameter used in study 120 is the urinary excretion over 72 hours by treatment, instead of the usual parameters used for the assessment of the bio-equivalence, namely T_{max} , C_{max} , T_{lag} , half-life or AUC parameters as recommended by the FDA or the European Agency for the Evaluation of Medicinal Products (see document (O17), page 6 and document (O19), page 7). The parameter gives only a general pharmacokinetic indication on the amount of risedronate which has been absorbed intestinally, since it also depends on the amount excreted by the renal function within 72 hours and is for these reasons not as accurate as the other parameters used, i.e. T_{max} , C_{max} , T_{lag} , half-life and AUC.

Moreover, the final result of 30% reduction between the fasted and fed administration amounts to a quantity of 70% of risedronate absorbed in fed state reported to be amount absorbed in the fasted state. This result of 70% of the urinary excretion between the fasted and fed administration is outside the equivalence limit of 80-125% generally recognized and defined by the FDA or the European Agency for the Evaluation of Medicinal Products (see document (O17), page 6 and document (O19), page 7). This result expresses explicitly that the administration of an enteric coated tablet with 35 mg of risedronate and 100 mg of disodium EDTA between the fasted and fed state is not bio-equivalent, and thus that the food effect has not been suppressed.

- (b) Additionally, study 076 of document (O11) shows the suppression of the food effect, when the molar ratio of disodium EDTA to risedronate is around 1:1, thus corresponding to the preferred molar ratio of document (O1). This study shows a comparison between an administration in fasted and fed state of delayed release compositions comprising respectively 75 mg of risedronate and 100 mg of disodium EDTA and 100 mg of risedronate with 100 mg of disodium EDTA, corresponding thus to a molar ratio of disodium EDTA to risedronate of around 1:1. The urinary excretion of risedronate within 72 hours amounts respectively to the proportions of 85 and 87% of risedronate absorbed in fed state reported to the amount absorbed in the fasted state. These results are within the equivalence limit of 80-125% recognized by the regulatory authorities,

demonstrating explicitly that the suppression of the food effect is not linked with a particular molar ratio of disodium EDTA to risedronate of at least 2:1.

The effective absorption of risedronate with or without food or beverage, i.e. the suppression of the food effect has thus not not been demonstrated for the claimed composition. There is no indication, let alone any argument by the appellant, for any particular technical effect arising from the selection of the dosage form, various compounds and their respective amounts defined in the present independent claims. It is thus not possible to conclude to the existence of an improvement over the prior art.

2.5.3 Further arguments of the appellant

The appellant argued that the bio-equivalence between the administration of the dosage form of the claimed invention in fasted and fed state was attained, since its reached a level of ratio of 70% of risedronate urinary excretion between fed and fasted state, which is within the level that the invention intended to reach, namely "*a fed exposure within about 50% of fasting exposure*" as disclosed in the description of the contested patent (see par. [0023]).

The Board could not share this opinion. The suppression of the food effect is determined by the comparison of the bio-equivalence of a dosage form administered in fasted and fed state. Said bio-equivalence has a given technical meaning and is characterised by the absence of a significant difference in bioavailability between the different administrations of dosage form. A ratio threshold of 50% between the fasted and fed

administration presents obviously a significant difference and cannot be considered to be synonymous of bio-equivalence, even without taking in consideration the standard equivalence limit of 80-125% generally used by the regulatory authorities.

- 2.5.4 Consequently, in the absence of any experimental evidence or arguments establishing a minimum plausibility, the presence of an improvement of the properties of the claimed dosage form over the dosage form of document (O1) has not been credibly demonstrated and the technical problem must be reformulated as the provision of an alternative dosage form comprising risedronate.
- In view of the information found in the examples of the contested patent, the board is convinced that the problem has been plausibly solved.

- 2.6 It remains to determine whether the solution was obvious to the person skilled in the art.

Document (O1) envisages the use of tablets as dosage forms, and indicates the amounts of biphosphonte and disodium EDTA to be incorporated in the dosage form (see point 2.2.4 above).

Consequently, the subject-matter of claim 1 of auxiliary request 1 turns out to be merely the result of multiple arbitrary choices lying within the routine activity of the skilled person faced with the objective problem of providing starting from the disclosure of document (O1) alternative dosage forms of risedronate.

- 2.6.1 Further arguments from the appellant

The respondent argued the existence of a technical prejudice to use EDTA in oral dosage forms at such high doses. The clinical unsuitability of using EDTA orally was further supported by document (A2) and document (A13) which is an Injunction Pending Appeal submitted to the United States Court of Appeal, wherein an employee of the pharmaceutical company Teva asserts that it was hard to believe that human oral dosage forms could contain 100 mg or more of EDTA. Therefore the skilled person would not be motivated to use EDTA at such a high dose and would not envisage the claimed solution of claim 1 of auxiliary request 1.

The Board could not share this opinion. Document (O1) addresses explicitly and clearly the problem of the oral toxicity of EDTA by mentioning document (A2) for this purpose (see page 3, first par.) and by solving the problem through the use of an enteric coating to avoid the release of the chelating agent in the stomach, where conversion into undesirable compounds takes place (see page 4, 1st par.). Moreover, as to the question of the existence of a technical prejudice, it is not enough that the opinion or idea is held by a limited number of individuals or that it is a prevalent view within a given firm, however large, such as in document (A13). The existence of a technical prejudice is normally demonstrated by reference to the literature or to encyclopaedias published before the priority date or by proving that, in relation to the technical solution, a relatively widespread error or misapprehension about the technical invention existed among skilled workers in the relevant field before the priority date of the patent in suit. This was not the situation in the present case.

2.6.2 Thus, the subject-matter of claim 1 of the auxiliary request 1 is obvious vis-à-vis document (O1). Consequently, auxiliary request 1 does not meet the requirements of Article 56 EPC.

2.7 Auxiliary request 1A - Inventive step

Since the subject-matter of claim 1 of auxiliary request 1A is identical to claim 1 of auxiliary request 1, the conclusion drawn previously for auxiliary request 1 applies mutatis mutandis.

Thus, the subject-matter of claim 1 of the auxiliary request 1A is obvious vis-à-vis document (O1) and auxiliary request 1 does not meet the requirements of Article 56 EPC.

2.8 Auxiliary request 2 - Inventive step

This request corresponds to the claims as granted. The subject-matter of claim 1 of auxiliary request 2 is thus broader than the subject-matter of claim 1 of auxiliary request 1.

Since the subject-matter of this request includes the subject-matter of auxiliary request 1, for which negative conclusions were reached as regard inventive step, the reasoning and conclusions apply mutatis mutandis to auxiliary request 2.

The subject-matter of claim 1 of the auxiliary request 2 is obvious vis-à-vis document (O1) and auxiliary request 2 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated