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Datasheet for the decision of 1 October 2013

Case Number: T 1723/10 - 3.3.01

Application Number: 05706666.4

Publication Number: 1723157

IPC: C07F9/58, A61K31/663, A61P19/00

Language of the proceedings: EN

Title of invention:
AMORPHOUS FORMS OF RISEDRONATE MONOSODIUM

Patent Proprietor:
Zentiva, k.s.

Opponent:
Pronovem

Headword:
Amorphous forms/ZENTIVA

Relevant legal provisions:
EPC Art. 87, 84, 83, 54, 56
RPBA Art. 15(3), 15(6)

Keyword:
Main request: novelty (no)
Auxiliary requests 1 and 2: clarity (no)
Auxiliary request 3: allowable

Decisions cited:

Catchword:

-

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Case Number: T 1723/10 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 1 October 2013

Appellant: (Patent Proprietor)	Zentiva, k.s. U kabelovny 130 Dolni Mecholupy 102 37 Praha 10 (CZ)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 June 2010 concerning maintenance of the European Patent No. 1723157 in amended form.**

Composition of the Board:

Chairman: A. Lindner
Members: L. Seymour
C.-P. Brandt

Summary of Facts and Submissions

I. European patent No. 1 723 157 was filed as application number 05 706 666.4, based on the international application published as WO 2005/082915, filed on 28 February 2005 and claiming priorities from three Czech patent applications, filed on 26 February 2004 (CZ 2004-292; designated below as P1), 8 July 2004 (CZ 2004-798) and 12 August 2004 (CZ 2004-880).

Claim 1 as granted reads as follows:

"1. The monosodium salt of 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid in an amorphous form, having the X-ray diffraction pattern showing characteristic broad obtuse peak at 2θ angles ranging from 15 to 25°, and, optionally, two sharp peaks at 2θ angles of 5.856 and 6.99°."

II. Reference is made herein to the following documents cited during the opposition/appeal proceedings:

(5) WO 01/56983

(6) WO 03/033508

(8) A A Licata, Exp. Opin. Invest. Drugs, 1999, 8(7), 1093 - 1102

(11) EP-A-1 571 152

(12) WO 2004/037252

(14) WO 2005/075487

(15) Test report filed with letter of 25 May 2009

III. Revocation of the patent in suit was sought pursuant to Articles 100(b) and 100(a) EPC, for lack of novelty and inventive step.

IV. In its interlocutory decision, the opposition division maintained the patent in amended form, on the basis of the auxiliary request filed at oral proceedings before the opposition division. Claim 1 of the main request filed with letter of 25 May 2009 was found to lack novelty under Article 54(3) EPC with respect to document (11) (as its B-publication).

V. Both parties to the opposition proceedings appealed against this decision.

VI. With its statement of grounds of appeal, the appellant patentee filed a main request and an auxiliary request, which were identical to those forming the basis of the decision under appeal.

Claim 1 of the main request is identical to claim 1 as granted (see above point I).

VII. With its statement of grounds of appeal, the appellant opponent raised objections with respect to the auxiliary request under Articles 123(2), 84, 83, 54 and 56 EPC.

VIII. In a communication dated 12 June 2013 sent as annex to the summons to oral proceedings, attention was drawn to certain additional points arising with respect to the auxiliary request under Articles 123(2) and 84 EPC.

IX. With its response of 29 August 2013, the appellant patentee filed auxiliary requests 1 to 4. The pending

auxiliary request was renumbered as auxiliary request 5.

Claim 1 of auxiliary request 1 reads as follows:

"1. The monosodium salt of 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid in an amorphous form, having the X-ray diffraction pattern showing characteristic broad obtuse peak ranging from 15 to 25° 2θ, and two sharp peaks at 5.856 and 6.99° 2θ, or having the X-ray diffraction pattern of Figure 4."

Claim 1 of auxiliary request 2 reads as follows:

"1. The monosodium salt of 3-pyridyl-1-hydroxy-ethylidene-1,1-bisphosphonic acid in an amorphous form, having the X-ray diffraction pattern of Figure 4 or of Figure 9."

Claim 1 of auxiliary request 3 differs from that of auxiliary request 1 in the deletion of the option "or having the X-ray diffraction pattern of Figure 4".

X. At the oral proceedings held before the board on 1 October 2013, the appellant opponent was not represented, as announced by letter of 7 August 2013.

XI. The appellant opponent submitted arguments in its statement of grounds of appeal with respect to the auxiliary request, which was subsequently renumbered as auxiliary request 5 (see above points VI and IX). Insofar as these arguments are relevant to the auxiliary requests dealt with in the present decision (i.e. auxiliary requests 1 to 3), they may be summarised as follows:

The compound claims that referred to figures failed to comply with the provisions of Article 84 EPC. This reference introduced ambiguity as to what the claims intended to cover, also in view of the lack of information as to the wavelength used to obtain the X-ray diffraction pattern depicted in Figure 4. There was a high probability that two different sources have been used in generating Figures 4 and 9, in view of the different positions of the peak maxima in the two diffractograms.

It was further argued that the method claims were insufficiently disclosed because these had been asserted to yield a different product despite the fact that the same starting materials and conditions had been used as in Example 3 of document (12) and in Example 1 of document (14). Therefore, it was clear that the method claims did not specify all the essential steps to allow the skilled person to prepare the products claimed. Moreover, essential structural features of the starting material were not defined in the claims.

In addition, the subject-matter claimed could not benefit from the first priority date of 26 February 2004. Therefore, documents (11), (12) and (14) were relevant to the question of novelty, and the forms disclosed in Figure 1, Example 3 and Example 1, respectively, were to be viewed as being novelty destroying. In this context, the appellant opponent argued that the sharp peaks defined in the claims related to impurities rather than a semi-crystalline form. Moreover, since the conditions used in the examples according to the prior art fell within those claimed, these must be assumed to yield the same product.

In its assessment of inventive step, the appellant opponent argued that the claimed subject-matter lacked an inventive step starting from document (5) or (8) in combination with document (6).

Risedronate, as disclosed in documents (5) and (8), was known to be a very promising drug from a class of bisphosphonates known to suffer from poor absorption.

It was common general knowledge that the amorphous form of a drug, having no crystalline lattice, required less energy for dissolution, so that its bioavailability was generally greater than that of the crystalline form. Moreover, in document (6), alendronate, another bisphosphonate, had been formulated in the amorphous form.

It would therefore have been obvious for the skilled person, faced with the problem of increasing the bio-availability and/or solubility of sodium risedronate, to modify the known salts accordingly. Thus, the skilled person would have expected the higher solubility of the amorphous form in water demonstrated in Example 11 of the patent in suit and in comparative test B of document (15).

Finally, the appellant opponent submitted that an inventive step could also not be based on Example 10 of the patent in suit or on comparative test A of document (15). These results could not be linked to polymorphism, since this was destroyed upon dissolution. Moreover, the results obtained were not comparable owing to the different dilutions of the crystalline and amorphous forms.

XII. The appellant patentee's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant patentee maintained that the priority date of 26 February 2004 based on P1 was to be acknowledged for the subject-matter of claim 1 of the main request relating to "an amorphous form, having the X-ray diffraction pattern showing characteristic broad obtuse peak at 2θ angles ranging from 15 to 25°". Both the patent in suit and the priority application P1 disclosed the same Example 1 referring to the same figures. Therefore, the same invention was to be found in both documents. The mere fact that said feature was not explicitly mentioned in P1 did not render the priority invalid, since Figure 4 of P1 exhibited a symmetric broad obtuse peak centred at a 2θ value of 20°, and beginning at 15° and ending at 25°, as clearly indicated by the division marks along the horizontal axis. The peak as claimed was therefore directly and unambiguously derivable from P1 as being characteristic for the present invention.

If priority were not to be acknowledged, than the same standard should be applied when judging whether the disclosure of document (11) was relevant to the issue of novelty. It was evident from the X-ray diffractogram according to Figure 1 of document (11) that the characteristic peak was located at a different position, namely, between 2θ values of 12.5 to 22° centred at 17°, and had a different shape than that of Figure 4 of the patent in suit. This profile could be clearly distinguished from that claimed in claim 1 of the patent in suit. Document (11) did not therefore anticipate the subject-matter claim 1 of the main request.

With respect to auxiliary requests 1 and 2, the appellant patentee argued that a reference to Figure 4 had been introduced into claim 1 in view of the objection as to the validity of the priority date of 26 February 2004. It was accepted practice in the field of polymorphs to refer to figures. Moreover, the diffractogram of Figure 4 provided a clear definition of the amorphous form claimed. There could be no doubt that Cu K_α radiation was to be employed in the measurement thereof, since it was the wavelength of choice in the field. Furthermore, it was the wavelength disclosed in Figure 9, and no alternative was proposed in the patent in suit. The diffractogram of Figure 4 could thus be compared without difficulty with other diffractograms. For example, it was evident that Figures 4 and 10 of the patent in suit were the same, and that they differed from Figure 1 of document (11).

With respect to auxiliary request 3, the appellant patentee submitted that the objection under Article 100(b) EPC was unfounded since clear and complete instruction was provide in the patent in suit to enable the skilled person to carry out the process and obtain the product as claimed.

On the question of novelty, the appellant submitted that the subject-matter claimed was novel over documents (11), (12) and (14). In particular, the X-ray diffraction pattern depicted in Figure 1 of document (11) did not exhibit any sharp peaks. Moreover, in Example 3 of document (12) and in Example 1 of document (14) different conditions had been used than in the present examples, and different products with different properties had been obtained.

With respect to the issue of inventive step, the appellant patentee started from document (5) as the closest state of the art, and defined the problem to be solved as lying in the provision of forms of sodium risedronate having a larger utilisable portion. The solution proposed in the patent in suit was the semi-crystalline form as claimed. The comparative examples provided in the patent in suit and in document (15) demonstrated that the problem had been solved under conditions that simulated gastric juice. This result could not have been predicted from the cited prior art.

XIII. The appellant patentee requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with its statement of grounds of appeal, or, alternatively, on the basis of one of the auxiliary requests 1 to 4 filed with letter of 29 August 2013, or auxiliary request 5 filed as auxiliary request with its statement of grounds of appeal.

The appellant opponent requested in writing that the decision under appeal be set aside and European patent No. 1 723 157 be revoked in its entirety.

XIV. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeals are admissible.

2. The oral proceedings before the board took place in the absence of the appellant opponent who was duly summoned but chose not to attend, as announced with letter of 7 August 2013. According to Article 15(3) of the Rules of Procedure of the Boards of Appeal (RPBA, see Supplement to OJ EPO 1/2013, 38 to 49), the board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, as foreseen by Article 15(6) RPBA.

3. *Main request, claim 1*

3.1 Claim 1 of the main request relates to the monosodium salt of risedronic acid in an amorphous form. This is further characterised in "having the X-ray diffraction pattern showing characteristic broad obtuse peak at 2θ angles ranging from 15 to 25°". Before the issue of priority and novelty can be addressed, it must be decided how this feature is to be construed.

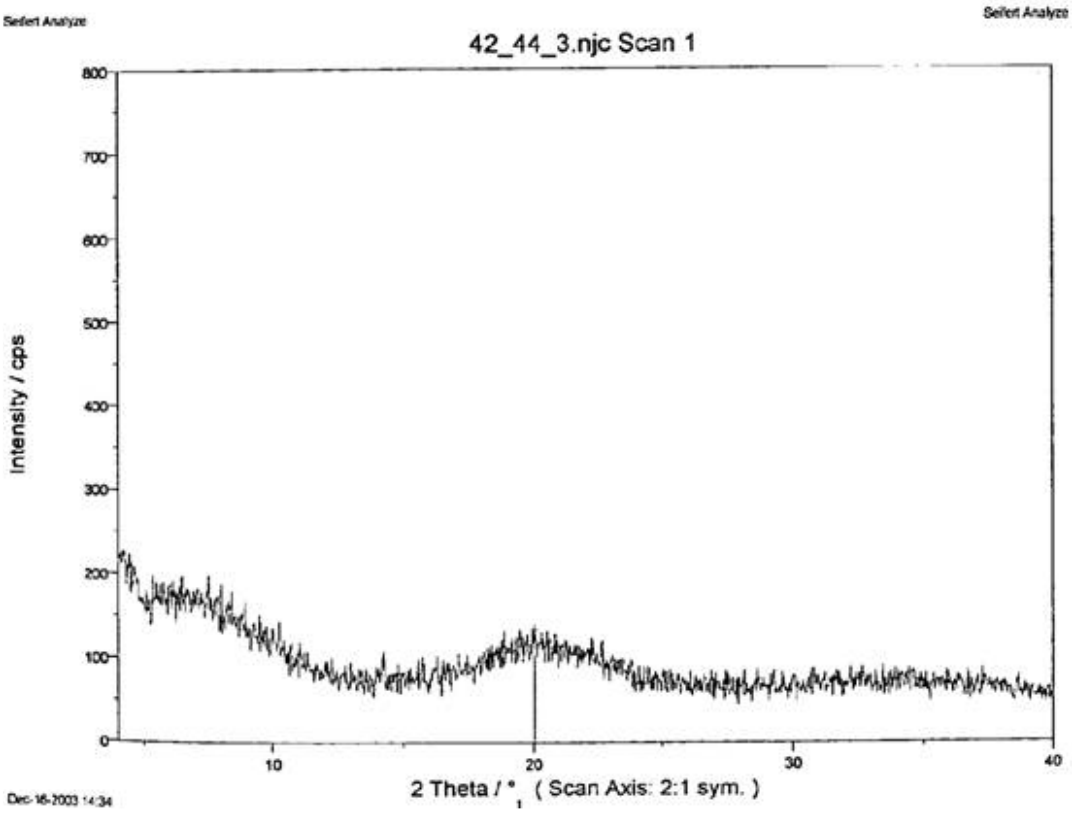
Dependent claim 2 refers to peaks "ranging from 17.4 to 20.2°", that is, covering only part of the range according to claim 1. Similarly, in the diffractogram according to Figure 9, the relevant peak is centred at a 2θ value of 17.6° (see also dependent claim 4), and, in so far as this can be judged in view of the overlapping peaks and the irregular base line, it is

asymmetric and only partially overlaps with the range specified in claim 1.

It must therefore be concluded that claim 1 is to be construed as relating to any amorphous form having at least one broad obtuse peak, which need not be symmetric in shape, positioned so as to lie within or partially cover the specified 2θ range of 15 to 25°.

3.2 *Priority (Article 87 EPC)*

3.2.1 The appellant patentee did not dispute that said feature of claim 1 is not mentioned *expressis verbis* in the present priority application P1 (cf. above point I), but argued that it was directly and unambiguously derivable from the following Figure 4 of this document:



The board observes that this figure relates to a complete diffractogram in the 2θ range between 0 and 40°, exhibiting several broad peaks of specific intensity and shape. The appellant patentee has not provided any convincing arguments as to why the skilled person would directly recognise any particular aspect of the above diffractogram as being the decisive feature, to the exclusion of all others, in characterising the amorphous forms claimed. The board cannot therefore accept that the above Figure 4 provides a basis for the more generally defined subject-matter of claim 1 (cf. above point 3.1).

3.2.2 The appellant patentee's arguments based on the division marks along the horizontal axis of Figure 4 are not considered to be convincing. Regarding the division marks at 15 to 25°, these are nothing but an indication of scale. It cannot therefore be accepted that they are intended to define the exact limits of any particular peaks. It is noted in this context that the peaks depicted run into each other on an irregular base line. It is therefore not possible to precisely determine where a given peak begins and where it ends. Moreover, the line extending from the division mark at 20° highlights a feature that it is not reflected in claim 1 of the main request, since the feature as defined in claim 1 is not limited to a symmetric peak centred at this 2θ value (cf. above point 3.1).

Finally, contrary to the appellant patentee's opinion, the relevant question to be answered is not whether some of the examples and figures are identical in P1 and in the patent in suit, but whether the more generally defined subject-matter of claim 1 of the main request is directly and unambiguously derivable from the priority document P1. For the reasons outlined

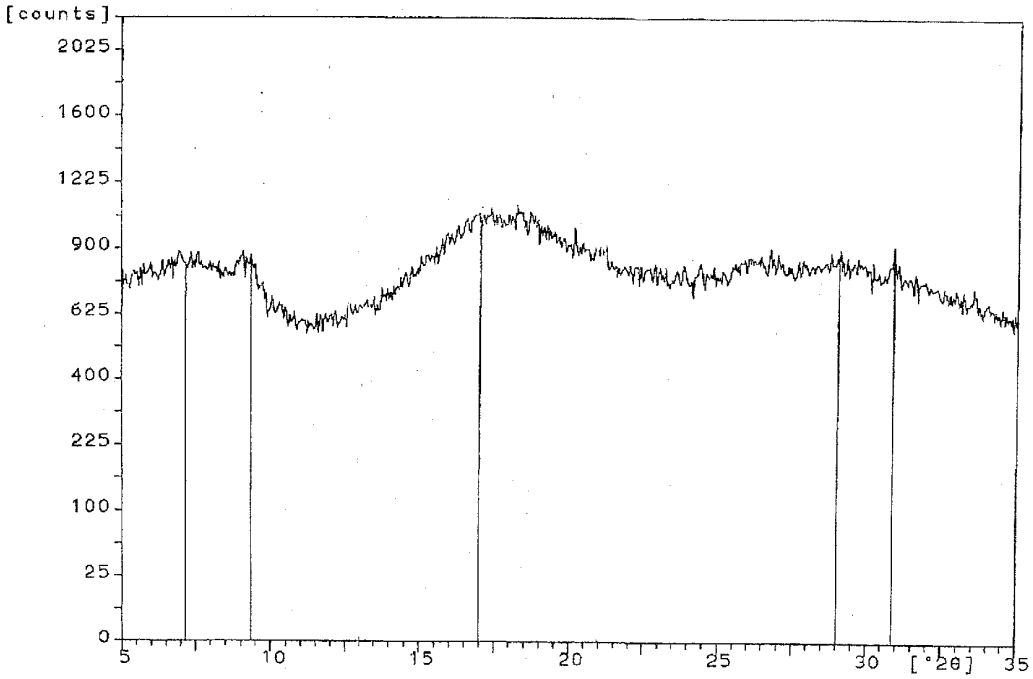
above, the board has come to the conclusion that this is not the case.

3.2.3 Consequently, the subject-matter of claim 1 of the main request is not entitled to the priority date of 26 February 2004.

3.3 *Novelty vs. document (11), Article 54(3) EPC*

3.3.1 It follows from the conclusion reached under point 3.2 above, and from the fact that document (11) is identical in content to its priority application US 60/558,908, which was filed on 1 April 2004, that document (11) enjoys an earlier effective date than claim 1 of the main request (cf. above point I). Document (11) is therefore to be considered as comprised in the state of the art relevant to the question of novelty, in so far as the same contracting states are designated (DE ES FR GB IT), pursuant to Article 54(3) EPC and Article 54(4) EPC 1973 (for transitional provisions of EPC 2000, see OJ EPO 2007, special edition no. 1, 197, Article 1, paragraph 1).

3.3.2 Document (11) relates to the monosodium salt of risedronic acid in an amorphous form, which is preferably prepared by a lyophilisation process to yield a powdered product having the X-ray diffractogram reported in Figure 1 (see paragraphs [0001] and [0011] to [0013], and claims 1, 3 and 4), which is reproduced below:



Although it is again not possible to precisely determine where a given peak begins and where it ends, it can be seen that the broad peak marked as being centred at a 2θ value of 17° covers a large part, if not all, of the range of 15 to 25°. Therefore, it is concluded that the product disclosed in document (11) exhibits all the features specified in claim 1 of the main request (see above point 3.1, last paragraph).

3.3.3 The board cannot agree with the appellant patentee's contention that the issues of priority and novelty are inextricably linked in the present case. As explained above in point 3.2, in the former case, it was to be decided whether Figure 4 of the priority document could provide a basis for claiming the more generally defined feature of claim 1. In contrast, the question at issue in the latter case is whether the diffractogram according to Figure 1 of document (11) falls within this more generally defined feature. These are clearly independent issues.

3.3.4 Consequently, the main request fails for lack of novelty of claim 1 with respect to document (11).

4. *Auxiliary request 1, clarity of claim 1*

4.1 According to one of the options of claim 1 of auxiliary request 1, the amorphous form is characterised by "having the X-ray diffraction pattern of Figure 4". Since this feature was not present in the claims as granted, it must be examined whether claim 1 so amended meets the requirements of Article 84 EPC. It is stipulated in Article 84 EPC that the claims shall define the matter for which protection is sought. Therefore, the question to be answered in the present case is whether the skilled person is able to derive a clear definition from claim 1 as to what is intended to be claimed.

It can be seen from Figure 4, which is the same as that reproduced above in point 3.2.1 from the priority application P1, that the diffractogram exhibits an irregular base line, peak overlap and a substantial amount of noise. Faced with this diffuse pattern, the skilled person is left in considerable doubt as to which specific features of the figure are intended to characterise and allow reliable identification of the amorphous form claimed.

This lack of clarity is further compounded by the fact that no details are given as to the conditions employed to obtain the diffractogram of Figure 4. In particular, depending on the wavelength of the radiation used, different X-ray diffraction patterns would be generated for the same sample. Therefore, in the absence of the relevant measurement conditions, it is not possible for

the skilled person to reliably establish whether a given amorphous form falls within the scope of claim 1.

In view of the above, it is concluded that the amorphous form claimed is not clearly characterised by the reference to Figure 4.

4.2 The appellant patentee's argument that Cu K_α radiation was to be employed in the measurement according to Figure 4 is not convincing. It is true that this wavelength has frequently been used, and specifically in generating Figure 9. However, many further sources are available, as outlined by the appellant opponent in its statement of grounds of appeal (page 3). There is therefore no basis for reading any restriction in this respect into Figure 4 of claim 1. It is further noted that the maxima of the broad peaks are at different positions in Figures 4 and 9, so that it cannot be assumed that the same wavelength was used to generate these two diffractograms.

In addition, the appellant patentee submitted that the diffractogram of Figure 4 could be compared without difficulty with other diffractograms, such as that of Figure 10 of the patent in suit, or Figure 1 of document (11). However, it can be seen from Figure 4 that a weak sharp peak is present at the 2θ value of about 14°, which is absent in Figure 10, or masked by noise. Uncertainty therefore arises as to whether these figures represent distinct amorphous modifications or not. Similarly, it cannot be established whether differences between Figure 4 of the patent in suit and Figure 1 of document (11) result from a difference in measurement condition or reflect differences in structure resulting from the different methods of production of the samples.

4.3 Consequently, the subject-matter of claim 1 of auxiliary request 1 is not clearly defined, contrary to the requirements of Article 84 EPC.

5. *Auxiliary request 2, clarity of claim 1*

Since claim 1 of auxiliary request 2 also contains a reference to Figure 4, the analysis provided above in point 4 applies equally to this request. Accordingly, auxiliary request 2 is not allowable under Article 84 EPC.

6. *Auxiliary request 3*

6.1 *Amendments (Articles 123(3), 123(2), 84 EPC)*

The amendments to this request mainly consist in the deletion of one of the options in the claims as originally filed and granted. In addition, independent method claim 6 is based on a combination of claims 14 to 17 as originally filed and granted.

It is therefore concluded that the amendments do not give rise to any formal objections Articles 123(3), 123(2) or 84 EPC.

6.2 *Sufficiency of disclosure (Articles 100(b), 83 EPC)*

6.2.1 Claim 1 relates to an amorphous form of sodium risedronate defined as having an X-ray diffraction pattern showing a broad obtuse peak and two sharp peaks.

General guidance with respect to suitable methods of preparation is provided in paragraph [0018], involving

"heating crystalline risedronate pentahydrate" under specific conditions (see also auxiliary request 3, claims 6 and 7). Examples 2 to 4 illustrate this process under various drying conditions, namely, "at 110°C for 20 hours", "at 50°C for 5 hours, then ... elevated to 100°C ... for 10 hours" and "under vacuum at 100°C for 10 hours", respectively. The X-ray diffraction pattern of the product prepared according to Example 2 is provided in Figure 9, which is specified as being measured using the Cu Ka wavelength and exhibits the features defined in claim 1.

Hence, the patent in suit contains all the information required to obtain the claimed amorphous forms of sodium risedronate.

6.2.2 The appellant opponent's arguments cannot cast doubt on this assessment for the following reasons:

Concerning the starting material to be used in the processes describe above, the pentahydrate is clearly defined in the patent in suit to be that according to document (12) (see patent in suit, examples 2 to 4, and paragraph [0008]). There can therefore be no doubt that the skilled person would be in a position to identify the required compound.

Moreover, the arguments of the appellant opponent with respect to Example 3 of document (12) and Example 1 of document (14) are also not convincing. Sufficiency of disclosure is to be assessed based on the patent in suit as a whole, that is, the claims and the description, including the examples. It is therefore not necessary, as argued by appellant opponent, that every combination of process conditions within the most general disclosure of the patent in suit would lead to

the claimed product, as long as sufficient guidance is provided as to how these can be modified in case of failure. In the present case, in Example 3 of document (12), the pentahydrate is dried in a vacuum oven at 105°C for six hours, and in Example 1 of document (14) at 50°C for five hours. In contrast, as outlined above in point 6.2.1, much longer drying times and, in the case of the latter, much higher temperatures are used in the examples according to the patent in suit. Based on this guidance, the board sees no reason to doubt that the skilled person would be in a position to select appropriate drying conditions in order to arrive at the products claimed without undue burden.

6.2.3 In view of the above considerations, the requirement of sufficiency of disclosure is considered to be met by auxiliary request 3.

6.3 *Novelty (Articles 52(1) and 54 EPC)*

6.3.1 In its statement of grounds of appeal, the appellant opponent maintained novelty objections with respect to document (11), Example 3 of document (12), and Example 1 of document (14).

The appellant patentee acknowledged that the subject-matter auxiliary request 3 is not entitled to the priority date of 26 February 2004, and that documents (11) and (14) are therefore to be regarded as state of the art pursuant to Article 54(3) EPC, and that document (12) is prior art under Article 54(2) EPC. The board sees no reason to differ with this assessment.

6.3.2 As outlined above (see above point IX), present claim 1 relates to an amorphous form of sodium risedronate

defined as having an X-ray diffraction pattern showing a broad obtuse peak and two sharp peaks. In contrast, the amorphous disclosed in document (11) does not display any sharp peaks in its X-ray diffractogram (cf. point 3.3.2 above), and cannot therefore be considered to be novelty destroying.

The appellant opponent's argument that the sharp peaks defined in present claim 1 merely related to impurities amounts to an unsubstantiated allegation, and must therefore fail.

6.3.3 In Example 3 of document (12), a product is produced that rapidly regains its original level of hydration on standing. According to the paragraph bridging pages 3 and 4, the crystal lattice is not disrupted under the drying regimes used. Similarly, the form produced in Example 1 of document (14) is crystalline. Since these products do not contain an amorphous component, it can be concluded that they would not exhibit a broad peak in their X-ray diffraction patterns, as required by present claim 1. Hence, these prior art products cannot be considered to destroy the novelty of the subject-matter claimed.

6.3.4 Consequently, the appellant opponent's novelty attack based on documents (11), (12) and (14) is not considered to be convincing.

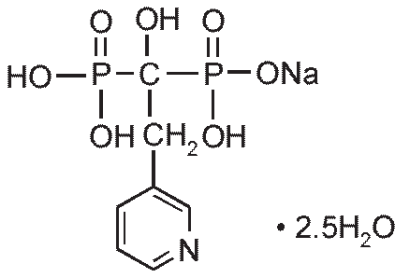
Accordingly, the subject-matter of auxiliary request 3 is considered to meet the requirements of novelty.

6.4 *Inventive step (Articles 52(1) and 54 EPC)*

6.4.1 The subject-matter of claim 1 is directed to the monosodium salt of risedronic acid in an amorphous form further characterised by a specific X-ray diffraction pattern. In the patent in suit, this form is also designated as being "semi-crystalline" (see paragraph [0016]). Risedronic acid belongs to a class of bisphosphonic acids is used in the treatment of bone diseases (see patent in suit, paragraph [0002]).

The board considers, in agreement with the appellant patentee, appellant opponent and the opposition division, that document (5) represents the closest prior art.

Document (5) discloses methods for the selective crystallisation of the hemipentahydrate or monohydrate of sodium risedronate (e.g. page 1, lines 11 to 14). The chemical structure of sodium risedronate hemipentahydrate is depicted in document (8) (page 1095) as follows:



According to the patent in suit (see paragraph [0005]), the monohydrate, which is also disclosed in document (5), spontaneously transforms to the stable hemipentahydrate. The latter can therefore be considered to be the more suitable starting point for assessing inventive step. It is further disclosed in

the patent in suit that, because the biological availability of salts of bisphosphonic acids is generally very low, the organism usually makes use of about 1% of the total mass of the active substance (see patent in suit, paragraphs [0011] and [0030]).

The problem to be solved, in the light of document (5), may therefore be defined as lying in the provision of forms of sodium risedronate having a larger utilisable portion.

The solution as defined in claim 1 relates to a specific amorphous form of the monosodium salt of risedronic acid.

6.4.2 As a next step, it has to be decided whether it has been rendered plausible that the problem defined above has been successfully solved by the claimed subject-matter.

The appellant patentee relied in this respect on the comparative examples provided in the patent in suit and in document (15).

Example 10 of the patent in suit provides a comparison of the dissolution behaviour in dilute hydrochloric acid for the known crystalline sodium risedronate hemipentahydrate according to document (5) and for the "semi-crystalline form" prepared according to Example 2 of the patent in suit (see paragraphs [0033] and [0047]). In both cases, a transparent solution was formed within 30 seconds. However, with the former, a white suspension started to precipitate within an additional 20 seconds, which did not dissolve upon further stirring. In contrast, with the latter, no precipitation was observed after 15 minutes. Similar

results were obtained in comparative test A of document (15).

It can be seen from the above data that the amorphous form according to present claim 1 exhibits improved solubility behaviour under conditions that simulate those prevailing in the stomach. As explained in paragraph [0034] of the patent in suit, it is important that sodium risedronate remains in the solution in the stomach, so that it can pass to the small intestine, where absorption takes place.

The appellant opponent challenged that said improvement in solubility could be truly linked to the solid-state form of the salts compared. However, this argument disregards potential kinetic aspects of the dissolution process, and must fail as being based on unsubstantiated allegations.

The appellant opponent also criticised the different "dilutions" of the forms compared. The board assumes that this a reference to differences in water content. However, it is noted that the water content of the form according to present Example 2 is 3%, and that of the corresponding form employed in comparative test A of document (15) is 1.6%. In both cases, comparable dissolution behaviour was obtained. There is therefore no reason to suppose that the precise water content of the claimed amorphous form has a significant influence on its dissolution behaviour.

In view of the above, and in the absence of any convincing evidence to the contrary, the board is satisfied that it has been rendered plausible that the problem defined above under point 6.4.1 has been solved by the subject-matter as defined in claim 1.

6.4.3 It remains to be decided whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

As outlined above under point 6.4.1, document (5) relates to the provision of crystalline hydrates of sodium risedronate. It does not suggest the use of an amorphous form in order to improve bioavailability.

The appellant opponent's attack with respect to inventive step relied on the common general knowledge that amorphous forms would be expected to be more soluble and have greater bioavailability than their crystalline counterparts. In this respect, the appellant opponent also referred to document (6) which discloses that an alendronate salt in an amorphous form dissolves in water at a faster rate than the crystalline material (see page 1, paragraph 5).

However, it is noted that this argument relates to expected solubility properties in water. There is no suggestion that this could be extrapolated to the behaviour of this class of compound under the acidic conditions found in the stomach. As can be seen from the structure reproduced above in point 6.4.1, sodium risedronate contains both acidic and basic moieties, which would complicate any predictions in this respect.

Hence, there is no hint in the cited prior art that the solubility problems under acidic conditions of the known crystalline hemipentahydrate of sodium risedronate could be solved by means of an amorphous form.

6.4.4 In view of the above, it is concluded that the subject-matter of claim 1 of the auxiliary request 3 involves an inventive step.

Claims 2 to 5 are dependent on claim 1, claims 6 and 7 relate to methods to the preparation thereof, and claims 8 to 10 are directed to corresponding pharmaceutical compositions. It is therefore concluded that the subject-matter of auxiliary request 3 meets the requirements of Articles 52(1) and 56 EPC.

Since auxiliary request 3 is considered to be allowable, the board need not decide on the lower ranking requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the third auxiliary request (claims 1-10) filed with letter of 29 August 2013 and the description to be adapted thereto.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated