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Datasheet for the decision of 19 March 2019

Case Number: T 1322/17 - 3.3.01

Application Number: 07014362.3

Publication Number: 1880744

IPC: A61P19/10, A61K31/663, A61K9/20, A61K9/28, A61K31/675

Language of the proceedings: EN

Title of invention:
Bisphosphonic acids for the treatment and prevention of osteoporosis

Patent Proprietor:
Atnahs Pharma UK Limited

Opponents:
Synthon BV
Avansor Pharma Oy
G. L. Pharma GmbH
Glenmark Pharmaceuticals s.r.o.
Stada-Arzneimittel Aktiengesellschaft
Laboratorios Liconsa, S.A.
Agrobiogen GmbH Biotechnologie
Actavis Group PTC EHF
Generica Ilac Sanayi ve Ticaret A.S.
Hexal AG
Gedeon Richter Plc.
ALIUD PHARMA GmbH / STADA Arzneimittel GmbH

Headword:
Ibandronate/ATNAHS

Relevant legal provisions:
EPC Art. 56, 54

Keyword:
Novelty - (yes)
Inventive step - (no) - all requests

Decisions cited:
T 0488/16, T 0715/03, T 0018/09, T 1014/07, T 0609/02, T 1329/04, T 1043/10

Europäisches Patentamt
European Patent Office
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Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1322/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 19 March 2019

Appellant 1: (Opponent 1)	Synthon BV Microweg 22 6503 GN Nijmegen (NL)
Appellant 2: (Opponent 2)	Avansor Pharma Oy Tekniikantie 14 02150 Espoo (FI)
Appellant 3: (Opponent 3)	G. L. Pharma GmbH Schlossplatz 1 8502 Lannach (AT)
Appellant 4: (Opponent 4)	Glenmark Pharmaceuticals s.r.o. Hve(zdova 1716/2b 140 78 Prague 4 (CZ)
Appellant 5: (Opponent 5)	Stada-Arzneimittel Aktiengesellschaft Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Prins, Hendrik Willem Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Appellant 6: (Opponent 6)	Laboratorios Liconsa, S.A. Gran Via Carlos III, 98, 7th floor 08028 Barcelona (ES)

Representative:
Schön, Christoph
Dr. Schön, Neymeyr & Partner mbB
Bavariaring 26
80336 München (DE)

Appellant 7:
(Opponent 7)
Agrobiogen GmbH Biotechnologie
Thalmannsdorf 25
86567 Hilgertshausen (DE)

Representative:
Becker, Eberhard
Patentanwälte
Becker, Kurig, Straus
Bavariastrasse 7
80336 München (DE)

Appellant 9:
(Opponent 9)
Generica Ilac Sanayi ve Ticaret A.S.
Yildiz Posta Cd. Dedeman Ishani 48/4 Esentepe
Istanbul (TR)

Representative:
Mutlu, Aydin
Invokat Intellectual Property Services Ltd.
Kartaltepe Mh. Yildiztepe Sk.
No:6-Bakirköy
34145 Istanbul (TR)

Appellant 10:
(Opponent 10)
Hexal AG
Industriestrasse 25
83607 Holzkirchen (DE)

Representative:
Hamm&Wittkopp Patentanwälte PartmbB
Jungfernstieg 38
20354 Hamburg (DE)

Appellant 11:
(Opponent 11)
Gedeon Richter Plc.
Gyömröi út 19-21
1103 Budapest (HU)

Representative:
Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Respondent:
(Patent Proprietor)
Atnahs Pharma UK Limited
Suite 1, 3rd Floor
11-12 St James' Square
London SW1Y 4LB (GB)

Representative:
Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München (DE)

Party as of right: (Opponent 8)	Actavis Group PTC EHF Reykjavikurvegur 76-78 220 Hafnarfjordur (IS)
Parties as of right: (Joint interveners)	ALIUD PHARMA GmbH / STADA Arzneimittel GmbH Gottlieb-Daimler-Strasse 19 / Muthgasse 36/2 89150 Laichingen / AT-1190 Wien (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 May 2017 rejecting the oppositions filed against European patent No. 1880744 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	L. Bühler

Summary of Facts and Submissions

I. European patent no. 1 880 744 was filed as patent application no. 07014362.3. It is a divisional application of the parent application no. 03722591.9 which was filed as an international application and published as WO 03/095029 (document (38)).

II. The present decision is based on the sets of claims of the main request and of auxiliary requests 1, 2, 2A, 3 (set of claims as granted), 3A, 4, 4A, 5 and 5A. These requests are referred to by their final numbering (see point VII below).

Claim 1 of the main request reads as follows:

"1. A medicament comprising 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof for use in the prevention or treatment of osteoporosis by administration as a single dose."

Claim 1 of auxiliary request 1 reads as follows:

"A medicament comprising 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof for use in the prevention or treatment of osteoporosis by administration as a single dose,
wherein the medicament is not a pharmaceutical composition containing:

Ibandronic acid	150.0 mg	
- as mono-sodium salt ($1H_2O$) of Ibandronic acid		168.75 mg
Povidone (K25)		22.5 mg
Lactose, monohydrate		162.75 mg
Cellulose, microcrystalline		60.0 mg
Crospovidone		22.5 mg
Stearic acid 95		9.0 mg
Silica, anhydrous colloidal		4.5 mg
Film-coat		
Film-coating mixture		12.75 mg
Macrogol 6000		2.25 mg.

"

Claim 1 of auxiliary request 2 reads as follows:

"Ibandronic acid or a pharmaceutically acceptable salt thereof for use in the prevention or treatment of osteoporosis, wherein 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof is administered as a single dose."

Claim 1 of auxiliary request 2A corresponds to claim 1 of auxiliary request 2 with the addition of the same disclaimer as defined in claim 1 of auxiliary request 1.

Claim 1 of auxiliary request 3 reads as follows:

"A medicament comprising 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof for administration as a single dose."

Claim 1 of auxiliary request 3A corresponds to claim 1 of auxiliary request 3 with the addition of the same

disclaimer as defined in claim 1 of auxiliary request 1.

Claim 1 of auxiliary request 4 reads as follows:

" A medicament comprising 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof for use in the administration as a single dose."

Claim 1 of auxiliary request 4A corresponds to claim 1 of auxiliary request 4 with the addition of the same disclaimer as defined in claim 1 of auxiliary request 1.

Claim 1 of auxiliary request 5 reads as follows:

" Ibandronic acid or a pharmaceutically acceptable salt thereof for use as a medicament, wherein the medicament comprises 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof and wherein the medicament is administered as a single dose."

Claim 1 of auxiliary request 5A corresponds to claim 1 of auxiliary request 5 with the addition of the same disclaimer as defined in claim 1 of auxiliary request 1.

III. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(3) US 6,143,326

(11) WO01/15703

(13) Krause, Chem Market reporter, December 17, 2001, Section 2, 1 page

(15) Riis et al., J Bone Mineral Res, 16(10), 2001, 1871-1878

(16) Bidstrup et al., Bone, 26(3), Supplement, 2000, 27S-42S

(18) Coleman et al., Annals of Oncology, 10, 1999, 311-316

(20) Ravn et al., Bone, 19(5), 1996, 527-533

(21) Ravn et al., Osteoporos Int, 9, 1999, 277-283

(22) Reginster et al., Ann Rheum Dis, 65, 2006, 654-661, download from internet on 9 February 2009, 22 pages

(41) Ravn et al., Bone, 30(1), 2002, 320-324

(46) Ravn, Danish Med Bulletin, 49(1), 2002, 1-18

IV. The appeals lie from the decision of the opposition division to reject the oppositions.

The respondent maintained its requests as filed before the opposition division. These requests (main request and auxiliary requests 1 to 5A) were re-submitted with its letter of reply.

V. Requests for acceleration were filed by the patent proprietor and by appellant 5.

The board granted the requests for acceleration.

VI. In a letter dated 26 June 2018, Aliud Pharma GmbH and Stada Arzneimittel GmbH filed a notice of joint intervention in the proceedings under Article 105 EPC.

VII. In a letter dated 18 February 2019 the proprietor renumbered and re-submitted its claim requests.

VIII. Oral proceedings were held before the board on 18 and 19 March 2019 in the absence of opponent 8 (party as of right), as notified by letter dated 26 September 2018.

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

Novelty

Neither document (3) nor document (11) disclosed, explicitly or implicitly, a dose of 150 mg ibandronic acid. Consequently, these two documents did not destroy the novelty of the subject-matter of claim 1 of the main request.

Inventive step

The closest prior art was document (20). Document (20) concluded that a daily dose of 2.5 mg ibandronate was the most effective dose. This conclusion was stated in the abstract and under the heading "conclusion". The appellants incorrectly interpreted the disclosure of document (20) with hindsight. A skilled person would not draw a different conclusion from a document than the authors of this document. Furthermore, the dose of 5 mg daily increased the prevalence of diarrhoea. Although generally diarrhoea might not be considered as a serious side effect, the situation was different for

the treatment of osteoporosis. Patients suffering from osteoporosis required long-term treatment, while feeling subjectively healthy. Side-effects that would noticeably worsen their quality of life would not be acceptable for them. The findings of document (20) were generally accepted, see documents (15), (16), (21), (41) and (46). Document (15) confirmed in particular that a skilled person would consider 2.5 mg ibandronate daily as the appropriate dose from which calculations in view of the total dose concept would be performed (abstract). Document (18) should be disregarded as it related to the treatment of cancer. In the treatment of cancer much more serious side effects were considered to be acceptable than in the treatment of osteoporosis.

The application as filed, in the paragraph bridging pages 3 and 4, explained its clear concept, i.e. using a higher amount of ibandronic acid than suggested in the prior art, see claim 6 as filed or page 6, lines 20 to 22 of the description as filed which describe preferred single doses of 100 to 150 mg ibandronic acid, and its administration on a monthly basis. As a result thereof, superior results were achieved. These results in the form of unexpected fracture reduction benefits (see page 4, lines 1 to 3), had been confirmed by the results of the MOBILE study, published in document (22). The inventors also had knowledge of further studies, conducted before the MOBILE study, i.e. the BONE and MOPS study, which formed the basis of the statements made in the paragraph bridging pages 3 and 4, as can be seen by the reference to the "ibandronate clinical development program" in this passage. The situation was thus similar to T 715/03. Unlike the situation in T 488/16, there were not a high number of compounds to be considered in the present

case, but only a single one. Furthermore, T 18/09 clearly stated that plausibility was only an issue when opponents had raised serious doubts substantiated by verifiable facts. Starting from the prior art, there was no reason for the skilled person, without hindsight, to administer 150 mg of ibandronic acid as a single dose (see T 1014/07). This dose of 150 mg, when prescribed properly by the physician, led to improvements in bone mineral density and thus fracture reduction benefits. These benefits had been proven in document (22) (page 10, first paragraph). In this context it was noted that the situation was different from the situation underlying T 609/02, in that the claim was very limited by defining one compound for the treatment of a defined disease.

The technical problem could thus be seen as defined by the opposition division: "How to provide a medicament that allows for a dosage regimen for osteoporosis treatment leading to unexpected fracture reduction benefit". Or, alternatively, as providing means for the treatment of osteoporosis having improved efficacy and patient compliance.

The solution claimed was not obvious. Starting from a daily dose of 2.5 mg ibandronic acid, there was no way of arriving at a dose of 150 mg ibandronic acid. As stressed before, a skilled person having knowledge of the intolerable side effects of a daily dose of 5 mg ibandronic acid, would not further consider this dose. Consequently, the calculations made by the appellants were made with hindsight. While the value of 150 mg could be reached, such theoretical considerations were not sufficient as a basis for a finding of obviousness (see T 1014/07).

The subject-matter of claim 1 involved an inventive step.

The same line of argument applied mutatis mutandis to the subject-matter of all the requests on file.

X. The appellants' and the interveners' arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Novelty

Document (11) related to the treatment of osteoporosis by intermittent dosage regimens. It disclosed a range of 3.5 to 200 mg of ibandronate to be administered (page 18, lines 16 to 20). The value of 150 mg ibandronic acid was well within this range. Since this value had not been shown to represent a purposive selection, the criteria of a selection invention were not fulfilled. The same applied to the disclosure of document (3), which disclosed a range of up to 250 mg ibandronate (column 5, lines 7 to 12). Consequently, these two documents destroyed the novelty of the subject-matter of claim 1 of the main request.

Inventive step

Documents (11) and (20) could be seen as the closest prior art documents.

Document (20) described two doses as equally effective, namely a daily dose of 2.5 mg and a daily dose of 5 mg. All side effects observed in the study underlying document (20) were considered to be not serious. Although there was a slight increase of diarrhoea in the 5 mg group, the skilled person would not have

disregarded the dose of 5 mg. As could be seen from document (15), the intermittent dosage regimen, relying on much higher daily doses, did not show a higher incidence rate of diarrhoea for these higher doses. The same could be derived from document (18). Consequently, the skilled person would seriously have considered 5 mg of ibandronate to be an effective and safe daily dose.

No technical effect could be linked to the value of 150 mg ibandronate. The claim under consideration neither defined a dosage regimen nor the mode of administration. The effect of fracture reduction benefits thus had to be ignored.

The technical problem could be seen as the provision of a medicament based on ibandronic acid as an active agent that could be used with a prolonged dosing interval going beyond daily administration for the prevention or treatment of osteoporosis.

The solution, i.e. the provision of a single dose of 150 mg ibandronic acid, was obvious. It was known from document (13) that Roche intended to market a once monthly oral medicament based on ibandronic acid for the treatment of osteoporosis (page 1, right-hand column, first paragraph). A person skilled in the art, with knowledge of the total dose concept (see document (15)) and starting from a daily dose of 5 mg ibandronic acid, in accordance with the closest prior art, would thus automatically arrive at a single dose of 150mg ibandronic acid (30 days x 5 mg).
The subject-matter of claim 1 was thus obvious.

The same line of argument applied to the subject-matter of the auxiliary requests.

XI. The final requests were as follows:

The appellants 1 to 7 and 9 to 11 (opponents 1 to 7 and 9 to 11) requested that the decision under appeal be set aside and that European patent No. 1 880 744 be revoked.

The joint interveners requested that European patent No. 1 880 744 be revoked.

The respondent (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request, or, alternatively, of any of auxiliary requests 1, 2, 2A, all filed with a letter dated 18 February 2019, or, alternatively, that the appeals be dismissed and the intervention be rejected (auxiliary request 3), or, alternatively that the patent be maintained on the basis of the claims of any of auxiliary requests 3A, 4, 4A, 5, and 5A, all filed with a letter dated 18 February 2019. The respondent further requested that auxiliary request 3 be admitted into the appeal proceedings.

Opponent 8 made no requests in appeal.

Reasons for the Decision

1. The appeals are admissible.

2. *Intervention*

The notice of joint intervention satisfies the requirements of Article 105 EPC and the Implementing Regulations. This was not disputed by the proprietor.

Thus, the joint intervention is admissible.

3. Oral proceedings were held in the absence of the duly summoned opponent 8 (party as of right) in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

4. *Main request*

4.1 *Novelty in view of documents (3) and (11) (Article 54(2) EPC)*

Two documents have been invoked as being novelty destroying for the subject-matter of claim 1 of the main request. Claim 1 of the main request is a second medical use claim in the form of a purpose limited product claim in accordance with Article 54(5) EPC. The prevention or treatment of osteoporosis is thus a technical feature that has to be taken into account when examining novelty.

Document (3) defines the treatment of bone disease with a tablet comprising 0.1 to 100 mg ibandronate (claim 1). Specific bone diseases, including osteoporosis, are defined in claim 3. A higher upper limit for administration as a single dose is described in column 5. There, the upper limit is set at about 250 mg ibandronate, however there is no mention of the specific disease to be treated (column 5, lines 7 to 12). The amount of drug to be administered depends on the specific disease under consideration. No specific single doses of ibandronate have been disclosed specifically in combination with the prevention or treatment of osteoporosis. To arrive at the claimed subject-matter, a certain disease has to be selected from the list described in document (3) and combined with a specific, not explicitly disclosed, amount of

ibandronate. This amounts to at least two selections. Consequently, the subject-matter of claim 1 is not directly and unambiguously disclosed in document (3).

Document (11) is slightly more specific than document (3). While the broadest range of ibandronate (about 3.5 mg to about 200 mg, see page 18, lines 16 to 20 or claim 4) is not associated with a specific disease, certain concentrations of ibandronate for the treatment of specifically osteoporosis are explicitly disclosed. Weekly oral dosages of 35 mg, 40 mg, 45 mg and 50 mg ibandronate are described for treating and preventing osteoporosis (page 19, lines 11 to 14). An amount of 150 mg ibandronate is not disclosed in this passage. Thus, a selection of the (not explicitly disclosed) value of 150 mg of ibandronate from the broader range of 3.5 to 200 mg on page 18 (see above), followed by a further selection of the specific disease, i.e. the prevention or treatment of osteoporosis, is necessary in order to arrive at the subject-matter of claim 1. Consequently, document (11) is not novelty destroying for the subject-matter of claim 1 of the main request.

4.2 *Inventive step (Article 56 EPC)*

The patent in suit relates to the use of bisphosphonic acids, especially ibandronic acid or pharmaceutically acceptable salts thereof for use in the prevention or the treatment of disorders characterised by pathologically increased bone resorption, in particular for the prevention and treatment of osteoporosis (paragraph [0001]). To this end a medicament comprising 150 mg of ibandronic acid or a pharmaceutically acceptable salt thereof for administration as a single

dose is claimed.

4.3 One of the documents that has been invoked as the closest prior art is document (20). Document (20) relates to a dose finding study for ibandronate in the treatment of postmenopausal osteoporosis (title). Document (20) states that 2.5 mg ibandronate daily is the most effective dose (abstract and page 532, last paragraph). When reading the body of document (20), it can be seen from several passages that a daily dose of 5 mg achieves the same therapeutic effects.

4.3.1 The respondent has argued that the skilled person would rely on the conclusion made by the authors of document (20) and consider that (only) 2.5 mg ibandronate was the daily dose.

The respondent has stressed that a skilled person would rely on the conclusion reached by the authors of a scientific article. Furthermore, a skilled person would take the lowest dose corresponding to the upper saturation plateau of a sigmoidal dose-response curve. They would not consider using a higher dose, since higher doses were considered to be linked to more side effects. This line of argument was also said to be backed up by the disclosure of documents (15), (16), (21), (41) and (46).

4.3.2 The appellants and interveners were of the opinion that a skilled person would consider the complete disclosure of a scientific article such as document (20). As several passages of this document stated that there were no serious side effects and that 5 mg ibandronate per day was as effective as 2.5 mg per day, the skilled person would consider 5 mg daily to be equally promising. Concerning the side effects, they argued

that any side effects were described as non-serious and that, furthermore, it was known from other documents, such as documents (15) and (18), that diarrhea was not more frequent at higher doses.

4.3.3 Document (20) focuses on dose finding. As can be seen from the "Results" section (page 529, right-hand column, second paragraph to page 531, right-hand column, penultimate paragraph), efficacy and safety have been assessed. Under the heading "efficacy", it is stated that responses in the groups receiving ibandronate 2.5 mg and 5 mg were not significantly different (page 529, right-hand column, paragraph 4). A similar statement is found in the "discussion" section (page 532, left-hand column, paragraph 3). Side effects are discussed under the heading "safety". It is stated in general that the safety evaluation did not reveal any differences between ibandronate and placebo treated groups (page 531, left-hand column, paragraph 1). While it is mentioned that none of the adverse events were considered serious, diarrhoea is identified as occuring more frequently in the 5 mg group (page 531, right-hand column, paragraph 1). This finding is repeated in the "discussion" section on page 532, right-hand column, paragraph 1.

4.3.4 Document (15) concludes that the efficacy of ibandronate depends on the total oral dose given rather than on the dosing schedule. Two dosing schedules are compared. The first dosing schedule provides the patient with 2.5 mg ibandronate per day. As a second approach intermittent dosing is tested. The intermittent dosage regimen relies on the administration of 20 mg ibandronate every other day for the first 24 days of every three month period, followed by 9 weeks without the active drug. Document (15) thus

teaches the administration of higher doses in an administration scheme that includes a longer dosing interval. The total doses are said to be similar (abstract). In fact the following calculation can be made: twelve times 20 mg divided by 90 days corresponds to 2.67 mg on a daily calculation base (12x20/90=2.67), which is indeed similar to the 2.5 mg daily administration of the second study arm. In document (15) this difference is acknowledged by referring to the total dose of 225 mg in the case of daily continuous administration versus 240 mg in the case of intermittent administration over a 3-month period (page 1872, right-hand column, second paragraph). In sum, document (15) teaches taking (approximately) multiples of about 2.5 mg per day to arrive at doses that are to be administered at a different - longer - dosing interval. It is reported that there was no difference in the side effects between the two regimens (page 1875, right-hand column, middle paragraph and figure 5).

Document (16) confirms the total dose concept, based on 2.5 mg per day or 20 mg ibandronate every second day for 12 doses for 3 months (abstract).

Document (21) states that 2.5 mg ibandronate or 10 mg alendronate are considered to be optimal doses for the treatment of postmenopausal osteoporosis (page 281, left-hand column, first paragraph). Document (21) does not relate to dose specific issues, but deals with methods for monitoring the effect on bone (abstract).

4.3.5 Document (41) presents the AUC data of a phase II clinical study of oral ibandronate. It concludes that "a dose of 2.5 mg ibandronate daily resulted in maximal depression of bone turnover, and although the serum

concentration almost doubled at 5 mg ibandronate perday, the clinical response in bone markers and bone mass did not increase further. This "threshold" pattern reflects a sigmoid-shaped logarithmic dose-response curve with a dose of about 2.5 mg ibandronate daily approaching maximal effect. The findings support the present recommendations of this dose being the lowest, most effective dose for treatment of osteoporosis in elderly women." (page 323, right-hand column, last paragraph). It thus confirms the findings of document (20) for daily administration.

Document (46) repeats the findings of document (20) and states on page 10, left-hand column, third paragraph, that 2.5 mg ibandronate per day was the lowest dose that caused an increase in bone mineral density and that there was no significant additional effect of the double dose of 5 mg ibandronate per day.

Documents (20), (41) and (46) are by the same first author and relate, in part, to the same clinical study. Document (16) seems to relate to the same clinical study as document (15).

4.3.6 In sum, these documents provide a clear picture. A daily dose of 2.5 mg is the minimal dose to be administered to achieve an effective treatment. The higher daily dose discussed, i.e. 5 mg per day, leads to higher plasma concentrations. Given daily, the prevalence of diarrhoea is higher for the 5 mg dose. When applying the total dose concept, which is generally established in the art (see for example documents (15) and (16)) and has been adopted by all parties, multiples of the daily doses are administered when longer dosing intervals are to be implemented. It can also be seen from the prior art (see documents (20)

and (15)) that diarrhoea is an issue predominantly of importance with daily dosing schemes.

Having studied the documents discussed above, the skilled person would not have discarded 5 mg ibandronate as an ineffective or unsafe daily dose. Daily doses of 2.5 mg and 5 mg ibandronate, described as effective in document (20), may form a starting point for considerations along the lines of the total dose concept.

4.4 The difference between claim 1 of the main request and the closest prior art is the considerably higher amount of 150 mg ibandronic acid or pharmaceutically acceptable salts thereof to be administered as a single dose.

As a next step it has to be determined whether the considerable increase in the amount of active agent leads to an unexpected effect.

The respondent has invoked the effect of "fracture reduction benefits", i.e. a reduced incidence rate of bone fractures. It has referred to the paragraph bridging pages 3 and 4 of the application as filed and to the post-published document (22).

4.4.1 It is established jurisprudence of the boards of appeal that the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. Post-published evidence that supports the fact that the claimed subject-matter solves the technical problem the patent in suit purports to solve may be taken into consideration, if it is already plausible from the

disclosure of the patent that the problem is indeed solved (see Case Law of the Boards of Appeal, 8th edition, I.D.4.6; T 1329/04, point 12 of the Reasons; T 1043/10, point 12 of the Reasons).

4.4.2 Thus, for post-published evidence to be taken into account, it is necessary to establish whether or not the asserted effect, in the present case the fracture reduction benefits, has been made plausible for the claimed subject-matter at the effective date of the patent in suit.

4.4.3 The application as filed describes in the paragraph bridging pages 3 and 4 that "Monthly oral treatment by administration of at least 120%, especially of 120% to 200% of the expected dose offers incremental patient benefits with respect to convenience and compliance as well as superior results. The "expected dose" (100%) corresponds to the cumulated efficacious daily doses. Prior to the completion of the ibandronate clinical development program, no bisphosphonate had prospectively demonstrated fracture reduction efficacy with a drug-free interval beyond daily administration. In summary, it is quite unexpected that fracture reduction benefit can be derived from a monthly administration of an oral bisphosphonate with a single or multiple tablet administration scheme." In sum, it is stated that a monthly oral dose (given as a single or multiple tablets), the dose to be calculated from the cumulated daily doses (amounts of ibandronate for this daily dose are not disclosed), and multiplied by a factor of between 1.2 and 2.0, leads to benefits with respect to convenience and compliance as well as superior results. Superior results are identified as being unexpected fracture reduction benefits. Furthermore, the paragraph makes reference to the

"completion of the ibandronate clinical development program". This program is not identified further. It is thus not clear which program is being referred to. Even if it was clear which program was referred to, a disclosure of the results of this program has not been included in the description and not made publicly available at or before the filing date. Results only known to the inventors derived from studies of unknown set-up (e.g. dosage regimen) cannot be considered when assessing the plausibility of certain effects.

Neither the paragraph reproduced above, nor any other passage of the application as filed provides experimental evidence. In this respect it is noted that as a matter of principle experimental evidence is not limited to clinical data. It is up to the parties, which evidence they consider appropriate for substantiating a certain fact. It is also noted that experimental evidence is not always necessary to render a certain effect plausible. A mechanistic explanation and/or common general knowledge may be sufficient in certain instances.

4.4.4 The description as filed recalls certain properties of bisphosphonates in general and of ibandronate in particular (page 2, line 1 to page 3, line 6). While reference to the ability of ibandronate to inhibit bone resorption without any impairment of mineralisation, to its ability to decrease osteoclastic activity and its ability to reduce the number of osteoclasts is made in the introductory passages of the description (paragraph bridging pages 2 and 3), no explanation is provided as to why a high oral monthly dose ("monthly" being described in the paragraph bridging pages 3 and 4, but not being a feature of claim 1 of the main request) would lead to greater fracture reduction benefits.

No line of argument involving common general knowledge has been put forward.

4.4.5 It is important to note that the disclosure of the paragraph bridging pages 3 and 4 and the subject-matter claimed in claim 1 of the main request differ in crucial aspects. While in the paragraph bridging pages 3 and 4 a specific dosing interval, i.e. one month, is described, this paragraph does not mention the amount to be administered and whether single or multiple tablet administration schemes are to be employed. In contrast to this paragraph, claim 1 does not define a dosing interval, but defines the very specific amount of 150 mg to be administered as a single dose.

4.4.6 In the application as filed, the unexpected fracture reduction benefits are neither supported by experimental evidence nor by a theoretical, possibly mechanistic, explanation. A mere statement that a certain effect arises (under conditions that are not reflected by the technical features of the claim under consideration), in the absence of any supporting circumstances, does not render the achievement of the effect by the technical features of the claim under consideration plausible.

4.4.7 Since a technical effect related to higher fracture reduction has not been made plausible for the specific dose of 150 mg ibandronic acid administered in any dosing interval in the application as filed, post-published evidence, in the present case document (22), cannot be taken into consideration. It is noted that it has not been questioned whether the administration of ibandronate can lead to the prevention or treatment of osteoporosis. The board's conclusions apply merely to

the plausibility of achieving higher fracture reduction benefits.

4.4.8 The respondent has invoked decisions T 488/16, T 715/03 and T 18/09 to strengthen its line of argument that the effect described in the paragraph bridging pages 3 and 4 must be taken into consideration in the assessment of inventive step:

According to the respondent, the application as filed, contrary to the situation in T 488/16, does not concern an extremely high number of compounds, but relates to a single compound. The respondent thus sees no reason to doubt the statements made in the paragraph bridging pages 3 and 4 and to disregard the post-published data in form of document (22).
The board considers the present situation to be different from the situation in T 488/16. Wherein in the description underlying T 488/16 a statement was made that the compounds were active, in the present case, due to the wording of claim 1, not even a statement clearly and directly linking the technical features of claim 1 to the alleged effect can be found in the description. The post-published data thus does not confirm a statement made in the description, but relates to technical effects based, at least partially, on technical features that have not been disclosed to be linked to the effect under consideration.

The respondent invoked T 715/03 to show that data known solely to the inventor can be used to render the presence of a technical effect plausible.
The board, again, stresses the fact that in the present case the technical feature, i.e. the amount of 150 mg ibandronic acid to be administered as a single dose, for which the technical effect allegedly arises, is not

even mentioned in the paragraph bridging pages 3 and 4. In the context of T 715/03 the board wants to point to another passage in decision T 715/03 which states that for the acknowledgement of an inventive step "it is a condition sine qua non that it is credible that the problem was plausibly solved at the priority date" (reasons 2.4.2).

T 18/09, in the context of industrial applicability, states that one aspect for consideration is whether the claims are commensurate with the level of disclosure. The board notes that it is a decisive aspect of the present case that the claim relies on a technical feature (the amount) that cannot be derived from the passage in the description relating to the effect under consideration. The standard of proof (i.e. serious doubts substantiated by verifiable facts) can only be considered/applied when there is a disclosure linking a certain technical feature to a technical effect.

4.5 Since the technical effect of a fracture reduction benefit cannot be acknowledged to be linked to the technical features defined in claim 1, the technical problem has to be formulated as follows:

The technical problem is the provision of a medicament based on ibandronic acid as an active agent that can be used with a prolonged dosing interval going beyond daily administration for the prevention or treatment of osteoporosis.

4.6 The solution is a medicament comprising 150 mg ibandronic acid or pharmaceutically acceptable salts thereof to be administered as a single dose.

A certain dosing interval is not part of the claimed

solution. The solution as defined in claim 1 of the main request relies solely on the single administration of the specific dose of 150 mg.

The problem is considered to be solved. It is generally known that ibandronic acid is a bisphosphonate suitable for preventing or treating osteoporosis. Also, due to the "total dose concept", which is generally accepted, it is credible that a higher amount of active agent will be effective when administered with a longer dosing interval.

4.7 It remains to be assessed whether the specific amount of 150 mg ibandronic acid is an amount the skilled person would have seriously contemplated. In the absence of a mandatory dosing interval this specific value for the amount of ibandronic acid to be administered has to be considered to be arbitrary.

When aiming to provide a longer dosing interval, the skilled person would look to the prior art for suggestions regarding the administration of bisphosphonates, especially ibandronic acid. In the present appeal proceedings, three documents have been invoked which point towards dosing intervals that go beyond daily administration. Apart from documents (11) (weekly, biweekly, bimonthly dosing intervals) and (15) (intermittent dosage regimen), document (13) has been submitted. Document (13), an article published in the "Chemical Market Report", describes the commercial activities and plans of pharmaceutical companies active in the field of osteoporosis. When discussing the company Roche, it is stated that this company is aiming to commercialise, as "more competitive formulations, an oral once-monthly and a quarterly IV" formulation of ibandronate (right-hand column, first paragraph). There

is thus a clear suggestion of a once monthly administration of ibandronic acid by the oral route. Furthermore, the idea of even longer dosing intervals, albeit for intravenous administration, is presented. The skilled person would take this disclosure as valuable information about which dosing intervals are feasible for ibandronic acid. The respondent has not contested that the skilled person would consider the dosing intervals suggested by document (13).

However, the respondent has argued that document (13) cannot lead a skilled person to the claimed subject-matter, since the absence of the disclosure of an amount of ibandronic acid meant that the crucial information was missing from document (13).

However, information concerning amounts is present in the closest prior art document, which relates to a dose-finding study. Also, the total dose concept is a concept which is well-established for bisphosphonates, and this has also been acknowledged by the respondent.

According to the total dose concept, the skilled person would make various straight forward calculations based on known daily doses of ibandronic acid. Possible dosing intervals known from the prior art are seven days (weekly of document (11)), 14 days (bi-weekly of document (11)), 30 days ("standard month", see document (13)) and 90 days (intermittent, see document (15)). One possibility open to the skilled person is to multiply the effective dose of 5 mg per day from the closest prior art document by 30 days, leading to a dose of 150 mg. There are however other ways of arriving at this dose. Since, as stated above, the amount of 150 mg ibandronic acid in the absence of a definition of a specific dosing interval is

arbitrary, it is sufficient to show that the value of 150 mg is one of the values the skilled person would reach by doing simple calculations based on the total dose concept. The value of 150 mg thus corresponds to one of many possible amounts the skilled person would consider when applying the total dose concept with an undefined dosing interval. No inventive step can be acknowledged.

4.8 The subject-matter of claim 1 of the main request does not involve an inventive step.

4.9 Further arguments:

4.9.1 The respondent has argued that any calculation leading to the value of 150 mg amounts to hindsight. A skilled person could arrive at the value of 150 mg, but would not necessarily do so. In this respect T 1014/07 has been invoked.

The board notes that claim 1 merely defines a dose which is not linked to a dosing interval and thus for the reasons set out in point 4.7 above is arbitrary. The established case law relating to the "could-would" approach thus cannot be applied.

4.9.2 Another argument presented by the respondent relied on the clear difference from the situation underlying T 609/02. Contrary to the situation in T 609/02, the claim under consideration was a very limited claim that defined a specific compound to be used in the treatment of a specific disease.

The board agrees that the present situation is different to the situation of T 609/02. However, due to these major differences, decision T 609/02 cannot

provide any guidance on how to deal with the plausibility of the effects in the present situation. The mere fact that a different situation exists does not necessarily render these effects plausible at the date of filing.

4.9.3 Concerning the preference for the amount of 150 mg, to be derived from the definition in claim 6 as filed ("the efficacious dose is about 150 mg") and on page 6, lines 20 to 22 as filed ("Preferably, the medicament comprises 100 to 150 mg of a ibandronic acid or a pharmaceutically acceptable salt thereof"), it has to be stated that these passages have to be seen in light of the disclosure as a whole. Claim 1 as filed, on which claim 4 is dependent, defines a dosage regimen (administered on one, two or three consecutive days per month) and not a single dose. The passage on page 6 cannot change the fact that the single passage in the description relating to the effect of fracture reduction benefits explicitly mentions a monthly administration and refers to single or multiple tablet administration schemes (see paragraph bridging pages 3 and 4). Consequently, the mention of specific amounts in another set-up (more limited by the restriction to a single dose, broader by the absence of a definition of the dosing interval) cannot influence the assessment of the paragraph bridging pages 3 and 4.

5. *Auxiliary requests - inventive step (Article 56 EPC)*

The same reasoning as given for claim 1 of the main request also applies to the respective claims 1 of all auxiliary requests. The subject-matter of said claims does not differ from that of the main request in a way that would change the reasoning of point 4 above which therefore also applies to the auxiliary requests.

The subject-matter of claim 1 of auxiliary requests 1, 2, 2A, 3, 3A, 4, 4A, 5 and 5A does not involve an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated