IN THE NAME OF THE KING

ruling

COURT OF APPEAL

Private Law Section
Case file number: 200.1 50.713/01
Case file number / docket number Court The Hague: C/09/460540 / KG ZA 14-1 $5

ruling of 27 January 2015

in the matter of:

the company under foreign law
Novartis AG,
with registered office in Basel, Switzerland
Appellant,
referred to herein below as: 'Novartis',
attorney: *Mr* D. Knottenbelt in Rotterdam,

versus

the close company with limited liability
SUN PHARMACEUTICAL INDUSTRIES (EUROPE) B.V.,
with registered office in Hoofddorp,
Respondent,
referred to herein below as: 'Sun',
attorney: *Mr* M.H.J. van den Horst in The Hague.

1. The suit

By writ of 6 June 2014 Novartis filed appeal of a judgment given by the judge in summary proceedings of the Court The Hague between parties dated 12 May 2014. By notice of appeal Novartis put forward seven grounds for appeal. By defence on appeal Sun challenged the grounds for appeal and filed an interim action ex article 234 Rv.[1] Sun subsequently withdrew its interim action.

[1] [Dutch] Code of Civil Procedure.

Thereupon parties had their cases pleaded on 4 December 2014, Novartis by *Mr* R.M. Kleemans and *Mr* A.A.A.C.M. van Oorschot, attorneys in Amsterdam, assisted by K.M.L. Bijvank (MSc), patent attorney and Sun by its attorney afore-mentioned, and *Mr* J.J.E. Bremer, attorney in The Hague, assisted by Dr *Ir* H. Prins, on both sides on the basis of filed pleading notes. Finally parties requested a ruling.

2. Facts

The facts established by the Court in the judgment of 12 May 2014 are not in dispute. The Court of Appeal shall likewise take these as its point of departure. The following is at issue in this matter.

2. 1 Novartis is a world-wide operating pharmaceutical company.

2.2 In the 1980s a legal predecessor of Novartis discovered the bisphosphonate zoledronic acid (also referred to as zoledronate). Novartis developed a medicine with zoledronic acid as active ingredient which is used in the oncological field, particularly in the treatment of tumour-related hypercalcaemia and the prevention of bone-related complications in patients with advance tumour disorders that had spread to the bones. For this indication Novartis commercialized the pharmaceutical product Zometa® as a 4 mg/5 ml concentrate for the preparation of an infusion solution.

2.3 Zoledronic acid was protected as an active ingredient until 16 May 2013 by the European patent EP 275 821 and the corresponding supplementary protection certificate 300058 for the product Zometa®.

2.4 Novartis currently commercializes the medicine Aclasta®, which, just like Zometa®, contains zoledronic acid as its active ingredient. Aclasta® is a 5 mg/100 ml solution for intravenous infusion that is administered once per year for the treatment of osteoporosis. Aclasta® is also approved as medicine for the treatment of Paget's disease (a rare chronic bone disorder that can lead to enlarged or malformed bones).

2.4 Novartis is holder of the European patent EP 1 296 689 (herein below also: EP 689 or the patent) for a "*Method of administering bisphosphonates.*" EP 689 was granted further to an application of 18 June 2001, with reliance on the priority documents US 597135 of 20 June 2000 (herein below: US 135) and US 267689 of 9 February 2001 (herein below: US 689). The grant of the patent for inter alia The Netherlands was published on 21 September 2005.

2.5 After application of the central limitation proceedings as referred to in article 105a ff. of the Convention concerning the grant of European patents (herein below: EPC) the (authentic) English text of the claims of EP 689 reads as follows:

1. Use of 1-hydroxy-2-(imidazol-1-yl)ethane-1, 1-diphosphonic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof in the preparation of a medicament for the treatment of osteoporosis in which the 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof is administered intravenously and intermittently and in which the period between administrations is at least about 6 months.
2. Use according to claim 1, wherein the period between administrations is at least about once a year.
3. Use according to claim 1, for the prophylactic treatment of osteoporosis wherein the period between administrations is about once per year or less frequent.
4. Use according to claim 1, for the prophylactic treatment of osteoporosis wherein the period between administrations is about once every 18 months, about once every two years or less frequent.
5. Use of 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof for the preparation of a medicament for the treatment of osteoporosis wherein said medicament is adapted for intravenous administration in a unit dosage form which comprises from about 1 up to about 10 mg of 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof, wherein the period between administrations of bisphosphonate is at least about 6 months.
6. Use according to claim 5, wherein the unit dosage form comprises from about I up to about 5 mg and the period between administrations is about once every 6 months.
7. Use according to claim 5, wherein the unit dosage form comprises from about 2 up to about 10 mg and the period between administrations is about once a year.

2.6 The undisputed Dutch translation of these claims reads: [translator's note: check original ruling for Dutch text].

2.7 On 29 July 2013 Sun obtained a market licence from the Medicines Evaluation Board (herein below: MEB) for The Netherlands with regard to generic zoledronic acid 5 mg/100 ml (RVG 11 1818) (herein below: generic zoledronic acid 5 mg/100 ml, or Generic Product). In the context of the application of that market licence Sun referred to Aclasta® as reference product. The market licence comprises approval of the product for the treatment of both osteoporosis and Paget's disease.

2.8 On 26 August 2013 Sun requested the CBG to remove the indication osteoporosis by means of a so-called "carve-out" from the SmPC (Summary of Product Characteristics) and the patient information leaflet for its generic product. The CBG informed Sun op 27 August 2013 that the application was processed. The policy of the CBG however sees to it that the carve out is not implemented in the digital version of the patient information leaflet and SmPC published by the CBG on its website.

2.9 Sun has had its generic zoledronic acid 5 mg/100 ml included in the G-standard of the company Z-index. The product has in the mean time become available in the Dutch market.

2.10 In October 2013 Sun registered for a so-called tender of healthcare insurer VGZ. By means of this tender procedure VGZ selected a number of preferential products, including a zoledronic acid 5 mg/100 ml product for patients to whim the infusion is administered at

home. Sun won the tender. This means that its generic product is the only zoledronic acid 5 mg/l00 ml product that is compensated by VGZ, except for medical necessity. The tender of VGZ made it impossible to register for the product zoledronic acid 5 mg/100 ml insofar as intended for a specific indication. The preference policy used by VGZ comprises that one single product is designated for any patient insured with VGZ that are treated at home with zoledronic acid in a dosage of 5 mg/100 ml, without distinguishing the indication for which it was prescribed.

2.11 In invalidity proceedings initiated by third parties against Novartis the English High Court found by judgment of 15 March 2013 ([2013] EWHC 516 (Pat)) that the British part of EP 689 cannot lay claim to the priority of US 135 and US 689 and that this part is therefore invalid on account of lack of novelty over an article published after the priority date, but before the application date of the patent by Reid (‘*A single annual injection of the bisphosphonate, zoledronic acid, stably reduces bone turnover and increases bone density in postmenopausal osteoporosis,*’ *Bone* 28(5), S89 (2001) herein below: Reid). By ruling of 19 December 2013 the English Court of Appeal upheld this judgment ([2013] EWCA Civ 1663).

Technical background

2. 12 The explanation herein below of the mechanism behind bone formation and bone resorption in general, the disease osteoporosis and Paget’s disease was largely derived from the unchallenged explanation by Novartis in the introductory summons in first instance.

2.13 Human bones consist of living tissue that is continuously regenerated during the life of an individual. Bone modelling plays an important role in the growth phase of young people. In fully grown adults bone remodelling becomes more important. Thanks to this mechanism which over a period ranging from seven to ten years results in a quantitative regeneration of the complete human bone mass, the skeleton remains stable and functional. Three types of cells in particular are involved in the bone remodelling process, to wit osteoclasts, osteoblasts and osteocytes. They are jointly referred to as bone remodelling units (‘BMUs’).

2.14 Bone tissue remodelling starts with osteoclasts that resorb bone tissue. In order to be able to do this they ‘dig’ into the bone matrix with the aid of different enzymes to form so-called resorption pits, which together form ‘grooves’ of resorbed bone material. Such resorption takes places at a rather fast rate, particularly because the osteoclasts have a small life cycle of only two to three weeks. The significantly smaller osteoblasts subsequently leave new collagen bone material (osteoid) behind in resorption pits, which gradually calcifies to form new bone. During this process some osteoblasts are enclosed by the mineralized bone matrix to differentiate later into osteocytes. The prevailing view on the priority date was that the bone remodelling cycle was largely completed after three to four months (see ‘*Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.’ An Official Publication of the American Society of Bone and Mineral Research,* 4th ed. 1999, p. 30).

2. 1 5 On the priority date it was known that bisphosphonates can inhibit resorption because they directly or indirectly influence the activity of osteoclasts negatively.

2.16 Osteoporosis is a frequent, often age-related, systematic bone disease in which the remodelling of the bone tissue is disturbed. In patients suffering from osteoporosis, more bone resorption than bone regeneration takes place. The most frequent form of osteoporosis is postmenopausal, but osteoporosis also occurs in men. All types of osteoporosis lead to frail bones that are more sensitive to fracture.

2.17 Paget's disease (*osteitis deformans*) is a local, chronic disorder that always leads in the affected bones to enlargements, malformations and deformations that undermine the bone. Paget's disease is caused by abnormal modelling and remodelling in specific places in the skeleton.

2.18 On the priority date two bisphosphonates were approved in The Netherlands for the treatment of osteoporosis, to wit, Didronel® (etidronate) and Fosamax® (alendronate). These preparations were in oral administration form and had to be taken on a daily basis.

3 The dispute

3.1 In first instance Novartis claimed after amendment of claim — in summary — that the judge in summary proceedings by judgment, as much as possible provisionally enforceable,
- forbids Sun to commit (indirect) infringement in The Netherlands of EP 689, more in particular by offering or supplying generic zoledronic acid 5 mg/l00 ml in The Netherlands, while it knows or should know that the product is going to be used for the treatment of osteoporosis,
- forbids Sun to take part in tenders/agreements for the supply in The Netherlands of generic zoledronic acid 5 mg/100 ml and forbids Sun to supply generic zoledronic acid 5 mg/100 ml under existing tenders/agreements, unless the tender/agreement is limited to treatment of Paget's disease,
- alternatively, forbids Sun to participate in tenders/agreements for the supply in The Netherlands of generic zoledronic acid 5 mg/100 ml, unless the tender/agreement is limited to treatment of Paget's disease, and forbids Sun to supply more than 135 units of generic zoledronic acid 5 mg/100 ml in The Netherlands under existing tenders/agreements,
- sentences Sun to keep administration of the sale of generic zoledronic acid 5 mg/100 ml in The Netherlands and to provide the attorneys of Novartis with a specification of that sale periodically,
- sentences Sun to inform all insurers that have floated a tender with regard to zoledronic acid 5 mg/100 ml or intend to do so as well as all parties that Sun concluded an agreement with in this respect or that approach Sun for this purpose, on the sentencing due to patent infringement and on the fact that Sun may exclusively supply zoledronic acid 5 mg/100 ml for the treatment of Paget's disease,

all of which on pain of a penalty and with sentencing of Sun in the full legal costs in accordance with article 1019h of the [Dutch] Code of Civil Procedure, herein below: Rv).

3.2 Novartis argued in this respect that the generic zoledronic acid 5 mg/100 ml product for which Sun obtained a market licence and that Sun had included in the G-standard is suitable and intended for the application claimed in claim 7 of EP 689, so that Sun commits infringement of that patent by offering and supplying this product.

3.3 The judge in summary proceedings rejected the claims of Novartis because in its preliminary opinion there is a serious likelihood that a judge in the proceedings on the merits will declare claim 7 of the Dutch part of the patent invalid. The judge in summary was of the provisional opinion that Novartis cannot rely on the priority of US 689 because the invention claimed in claim 7 of the patent is not directly and unambiguously disclosed in US 689. This leads to claim 7 of EP 689 lacking novelty in the light of Reid.

3.4 With the grounds for appeal put forward Novartis files appeal of the judgment in summary proceedings that Novartis cannot rely on the priority of US 689 and the grounds for appeal serve to have the Court of Appeal assess the dispute in its entirety. On appeal Novartis claims that its claims are allowed as yet, while sentencing Sun in the costs to be estimated in both instances on the basis of 1019h Rv.

4. Assessment

Reliance on priority of US 689 – novelty

4.1 The criterion for the assessment whether Novartis is entitled to priority of US 689, or that in that document, taken in its entirety, the invention claimed in claim 7 of the patent is directly and unambiguously disclosed to the person with average skill in the art, making use of his common general knowledge of the art.[2] The claimed invention must have been disclosed in a sufficiently enabling manner, in the sense that it must be plausible that the claimed invention works, or in other words: solves the problem.

4.2 It is not in dispute that the person with average skill in the art is a fictitious reference person consisting of a team of skilled persons, in any case consisting of a physician specialized in the field of the treatment of bone disorders and a pharmacologist that has experience in the development of pharmaceutical products for the treatment of bone disorders.

4.3 Departing from the said criterion the Court of Appeal, other than the judge in summary proceedings and the English High Court and Court of Appeal, partly because of

[2] Refer in that connection to the Enlarged Board of Appeal of the European Patent Office in G 2/98 and the decision of the Technical Board of Appeal in 1190/99.

different insights (more in particular after reading of the priority document) and partly because of other arguments of parties (including the common general knowledge of the art of the person with average skill in the art on the priority date), is for the time being of the opinion that Novartis is entitled to the priority of US 689.

4.4 The skilled person reading US 689 will pay special attention to Example 5 described in there, 'Treatment of Patients,' because this pertains to the results of a clinical trial. The skilled person will understand from the said Example 5 that it may be assumed that (also) one-off intravenous administration of 4 mg zoledronic acid during a period of 12 months is active in the treatment of postmenopausal osteoporosis (also refer to Reason 4.9 herein below). The skilled person will expect that a certain range around this will be active as annual dosage.

4.5 In the last paragraph of page 8 running into page 9 of US 689 a dosage range is mentioned for zoledronic acid for (inter alia) of a once annual dosage of about 2 to up about 10 mg. This paragraph reads as follows:

> *"For example, for more potent, recent bisphosphonates such as zoledronic acid a unit dose of from about 1 up to about 10 mg may he used. For example, also for such recent, more potent bisphosphonates a unit dose of from about 1 to about 5 mg may be used for dosing once every 6 months; whereas a dose of from about 2 up to about 10 mg may be used for once a year dosing."*

As the judge in summary proceedings observed, no explicit connection is made in this paragraph itself between that dosing range and intravenous administration. Other than the judge in summary proceedings the Court of Appeal is however of the opinion the skilled person, who considers the document in its entirety, while making use of his common general knowledge of the art, will find a certain degree of extrapolation in there of the dose of 4 mg once per year intravenously administered as disclosed in Example 5. The Court of Appeal also takes into consideration that it is not in dispute between parties that on the priority date it was part of the common general knowledge of the art of the skilled person that zoledronic acid was only administered intravenously.[3] It was likewise part of the common general knowledge of the art of the person with average skill in the art that the absorption in oral administration of bisphosphonates such as zoledronic acid was very low (1%) as opposed to full (100%) absorption in intravenous administration, so that in oral administration much more (100 x as much) must be administered to obtain the same effectiveness.[4] Given the dose administered intravenously of 4 mg once per year disclosed in Example 5, the dosing range mentioned on pp. 8/9 of US 689 of 2-10 mg once per year can therefore in all fairness only be understood thus that this pertains to intravenous administration. In oral administration the

[3] See par. 120 Defence on Appeal, par. 44 statement Dr Pazianas, party expert on the part of Sun.
[4] Par. 41 statement Dr Pazianas, par. 61 pleading notes Sun appeal proceedings.

skilled person would after all expect a dose in the range of 400 mg in view of the difference in absorption over intravenous administration.

4.6 The view of Sun that the dosing range of 2-10 mg once per year could also pertain to oral administration in the absence of explicit mention of the form of administration, is not a meaningful interpretation of the priority document in the provisional assessment of the Court in view of the above. The skilled person will dismiss the possibility of oral administration as unrealistic because zoledronic acid was never administered orally, but exactly always intravenously and he would moreover not expect that oral administration of only 2-10 mg zoledronic acid once per year would have effect, in view of the 100-fold difference in absorption and effectiveness.

4.7 The circumstance that in US 689 (p.7, last par.) the intra-arterial form of administration is mentioned as the most preferred form of administration, cannot detract from the above. As stated at the session by the experts on both sides, the skilled person will recognize that no difference is to be expected between intra-arterial administration and intravenous administration as to clinical effectiveness of the administered substance (and therefore does not make any difference as to dosing range). That the — riskier— intra-arterial administration form is nevertheless mentioned as the most preferred form will not be understood by the skilled person, but given his common general knowledge of the art that zoledronic acid is administered intravenously, this will not point him in another direction (than the idea that the dosing range of 2-10 mg pertains to intravenous administration).

4.8 All of the above leads to the conclusion that in the provisional opinion of the Court of Appeal, the skilled person, making use of his common general knowledge of the art, who considers the priority document US 689 in its entirety with a mind willing to understand, can directly and unambiguously derive the invention claimed in claim 7 of the patent from US 689.

Reliance on priority of US 689 — sufficiency of disclosure

4.9 Sun has argued that a claimed invention must have sufficient enabling disclosure in the priority document. It is however up to Sun then to make it plausible that this would not be the case. It must be put first and foremost that in the provisional assessment it follows from Example 5 of US 689 to a sufficient degree that it is plausible that intravenous administration of 4 mg zoledronic acid once per year is effective for the treatment of menopausal osteoporosis. On page 16 of US689 it is mentioned: "*The BMD data indicate that zoledronic acid dose administration as infrequent as every 6 or 12 months can safely result in a statistically significant and medically relevant bone mass increase*." There are no pointers that this would be different for the other doses within the range of 2-10 mg. On the contrary, it rather follows from the arguments of Sun that this is indeed the case. The party expert on

the part of Sun[5] argued that on the basis of the total dose principle a dose of 0.5 mg once per 3 months (which dose is presumably also effective according to Example 5) can be equated to a dose of 2 mg once per year, the lower limit of the range. The sufficiency of disclosure of the upper limit is encompassed by the argument of Sun that the skilled person would derive from Sorbera (‘*Use of Zoledronate Disodium for the treatment of tumour-induced hypercalcaemia — angiogenesis inhibitor,’ Drugs of the Future*, 25 (3,), March 2000) that a monthly dose disclosed in there of 4 to 8 mg zoledronic acid during 3 months would point the skilled person on the basis of that same principle to the direction of a yearly dose (of at least 12 mg). In the light of these arguments of Sun (whatever the correctness thereof, which will be discussed in more detail herein below), it has failed to make it plausible that the range of 2-10 mg per year has not been disclosed in a sufficiently enabling manner.

4.10 Other than argued by Sun the requirement of sufficiency of disclosure in the priority document does not comprise that it is plausible that the invention from being effective is also safe. After all, no safe(r) application is claimed in claim 7. It is established case law that clinical data need not be incorporated into a patent application. The conclusion is therefore that the position of Sun, that the invention claimed in claim 7 of the patent does not have sufficiency of disclosure in the priority document, must be denied for the time being.

4.11 It follows from the above that the grounds for appeal of Novartis are successful and that in the provisional opinion of the Court of Appeal Novartis is entitled to reliance on the priority of US 689. It is not in dispute that if Novartis can assert the priority of US 689, the publication of Reid does not belong to the prior art and is therefore not novelty-destroying.

4.12 In view of the devolutive effect the Court of Appeal has now arrived at the treatment of the other defences put forward by Sun.

Inventive step

4.13 Sun has based its inventive step attack on EP 689 on the problem-solution approach with WO 95/30421, published on 16 November 1995 (herein below: WO 421) as the closest prior art. The Court of Appeal considers that this patent application pertains to the use of bisphosphonates or the prevention of the loosening of the migration of prostheses (an acute, local disorder). In WO 421 osteoporosis is mentioned on page 1, last paragraph, as disorder that is treated with bisphosphonates: ‘*bisphosphonates, are used clinically to inhibit excessive bone resorption in a variety of diseases such as tumour-induced osteolysis, Paget’s disease and osteoporosis.”* Further on it is exclusively referred to osteoporosis in relation to the suggested broad dosing range of the said bisphosphonates for the treatment of a loosened or migrating prosthesis: *doses which are in the same order of magnitude as those used in the treatment of the diseases classically treated with methanebisphosphonic acid derivatives, such as Paget’s disease, tumour-induced hypercalcaemia or osteoporosis*, p.7, 4th par.). In

[5] Par. 21 statement Dr Pazianas.

WO 421 (p.7, 3rd par.) furthermore, only referring to the earlier-mentioned very broad dosing range in general and in connection with the prevention of loosening or migration of a prosthesis, possible dosing intervals are mentioned varying from once per day to once per year (for that matter without WO 421 comprising information on the basis of which the skilled person would consider it plausible that administration once per year would actually be effective and in WO 421 it is opted for once-off administration with possible repeats after 4 and 8 weeks, p. 2 last par.).

4.14 Stating from WO 421 the differential measures over claim 7 of the patent are: (1) specific zoledronic acid (WO 421 mentions many bisphosphonates and zoledronate and pamidronate as preferred bisphosphonates), (2) the indication osteoporosis, (3) the dosing range of 2-10 mg and (4) the dosing interval of one year. In view of these differential measures the problem must be formulated as the search for (a) different effective application(s) of bisphosphonates. The problem formulated by Sun, to wit, finding the dosing quantity and dosing frequency of zoledronate in the treatment of osteoporosis, cannot be accepted as being correct because this already includes the choices for both specifically zoledronic acid and for the treatment of osteoporosis.

4.15 Presuming the correctness of WO 421 as point of departure (which has been challenged by Novartis) the Court of Appeal is of the provisional opinion that the inventive step attack fails. Sun has failed to make it sufficiently plausible that the skilled person would have a pointer on the basis of which he would arrive on the priority date, starting from WO 421, without inventive conceptual labour at the application of specifically zoledronic acid for the treatment of osteoporosis by means of intravenous administration in a dosing range of 2-10 mg and a dosing interval of one year. The following reasons are given for this.

4.16 In the handbook of Fleisch (‘*Bisphosphonates in Bone Disease — from the Laboratory to the Patient,*’ 4th ed., 2000, p. 43), which represents the common general knowledge of the art of the skilled person on the priority date, the following is inter alia mentioned on the operative mechanism of bisphosphonates:

> *“The bisphosphonates can influence osteoclasts either directly as a result of their cellular binding or intracellular uptake, as well as indirectly via other cells. The direct effects are made possible by the uptake of these compounds by the osteoclasts during the resorption process, a process favoured by the fact that the bisphosphonates also deposit preferentially under the osteoclasts where they can attain very high concentrations, in the range of 10-4 or higher.”*

4.17 It was assumed that bisphosphonates, because they position under the osteoblasts, are encapsulated as soon as new bone is produced, which happens in cycles of 3-4 months, and that bisphosphonates could indeed be present in the skeleton for years after administration, but that once encapsulated in the bone bisphosphonate was inactive, as noted by Fleisch op p. 143 of his handbook: “*These results suggest that the bisphosphonate buried in the bone is*

inactive." That same mechanism is mentioned in the literature review of Fleisch on pp. 82-83 (‘*Bisphosphonates: Mechanisms of Action,’ Endocrine Reviews* 19(1). 80-100, 1998:

> *“In view of the accumulation of the bisphosphonates in bone, it is of great clinical interest that the inhibition of bone resorption reaches a certain steady level even when the compounds are given continuously. This level depends on the administered dose. This has also been described in humans. These results show that there is no accumulation of effect with time and suggest that the bisphosphonate buried in the bone is inactive, at least as long as it remains buried there.”*

4.18 On the effect of bisphosphonates after administration has ceased, Fleisch observes on p. 148 of his handbook that “*In general, bone turnover increases again within 3 months and reaches pre-treatment levels within a year*.”

4.19 On the priority date the idea prevailed therefore that the dosing interval in the treatment of osteoporosis should in any case not take longer than the total bone remodelling cycle of three to four months. Illustrative in that connection is the literature review of Miller (‘*Optimizing the Management of Postmenopausal Osteoporosis with Bisphosphonates: The Emerging Role of Intermittent Therapy’, Clinical Therapeutics,* Vol. 27, no. 1, 2005) that dates from after the priority date. In thirteen of the fourteen cited studies into the use of bisphosphonates for the treatment of osteoporosis a dosing interval of 3 months is used; the only exception concerns the research by Reid, which led to the invention in accordance with claim 7 of the patent.

4.20 None of the publications cited by Sun reliably shows the skilled person that at an interval of one year sufficient effectiveness can be expected from zoledronic acid for the treatment of osteoporosis.

- The tables of Figure 2 in the publication by Khan (‘*Elimination and Biochemical Responses to Intravenous Alendronate in Postmenopausal Osteoporosis,’ Journal of Bone and Mineral Research,* Vol. 12, no. 10, /997) on a clinical study into the effects of alendronate in administration to osteoporosis patients provide a trend that is difficult to interpret and ostensibly irreconcilable to the skilled person in the first period of 1-15 days on the one hand and that in the subsequent period of 1-24 months on the other hand, so that the skilled person would consider these data as insufficiently reliable and would therefore ignore them. The publication by Vasikaran (‘*Sustained Response to Intravenous Alendronate in Postmenopausal Osteoporosis’, Bone* Vol. 17, no. 6, December 1995:517-520) shares the same fate because this describes the same study.

— In Heikkinen (‘*Short-Term Intravenous Bisphosphonates in Prevention of Postmenopausal Bone Loss,’ Journal of Bone and Mineral Research,* Vol. 12, no. 1, 1997), a study into the use of clodronate in osteoporosis patients, the author himself suggests a dosing interval of 3 months: *“an optimal dosage might be intravenous infusion repeated four times per year*.”

- Lunar News (April 1997) is not a scientific journal. With reference to various publications (including Vasikaran and Heikkinen) non-researched and contradictory suggestions are made in there (on the one hand a high dose of a (non-specified) potent bisphosphonate once or twice per year, on the other hand a low dose of ofalendronate with reference to the fact that this would be the preferred form of administration of ibandronate). The skilled person would not attach any value to those unfounded suggestions.
— In Filipponi (‘*Intermittent Versus Continuous Clodronate Administration in Postmenopausal Women with Low Bone Mass,’ Bone* Vol. 26, No.3, March 2000, 269-274) the difference in effectiveness is examined from continuous versus once per half year administration of clodronate in osteoporosis patients and it is concluded that lower, but continuous administration has more effect. Although not researched, it is suggested that an administration of 1200 mg with an interval of 4 months could have optimum effect.
— In Thiébaud (‘*Three Monthly Intravenous Injections of Ibandronate in the Treatment of Postmenopausal Osteoporosis’, The American Journal of Medicine*, Vol. 103 (1997)) ibandronate is administered in a clinical study on a monthly or three-monthly basis to osteoporosis patients. It can be deduced from Figure 3 is that the effect of ibandronate already decreases after one month and that it has to a large extent become inactive after three months. It is suggested by the authors to apply a dosing interval of 3 months.
- Even apart from the scientific objections attached to the publication of Boutsen (abstract, ASBMR-IBMS Second Joint Meeting, 5313 (1998)), the skilled person would understand from this that a three-monthly dose (administered to patient group B) yields the best results: “*A sustained decrease was only observed throughout in group 3.*”

4.21 The Court of Appeal is of the provisional opinion that it is not to be assumed that the person with average skill in the art would be induced on the priority date by one of these publications, in spite of his knowledge of afore-mentioned operative mechanism of bisphosphonates, to use an interval of one year in the treatment of osteoporosis. They rather confirm the prevailing view that bisphosphonates must be administered at least once per bone remodelling cycle (which lasts 3-4 months). The single circumstance that there might have been a strong need for reducing the dosing frequency does not suffice.

4.22 Also, all above-mentioned publications cited by Sun pertain to other bisphosphonates than zoledronic acid. On the priority date so much was still unknown on the mechanisms underlying bone resorption and the exact effect of bisphosphonates on this. The skilled person knew that results attained with the one bisphosphonate were not predictive just like that for other bisphosphonates. Fleisch is very clear on this in his handbook, p. 30:

> *“Each bisphosphonate has its own physicochemical and biological characteristics. This variability in effect makes it impossible to extrapolate with certainty from data for one compound to others, so that each compound has to be considered on its own, with respect to both its use and its toxicology.”*

4.23 The publications that Sun also cited pertain to other indications than osteoporosis and — except for Body 1997 (‘*Clinical Research Update Zoledronate’, Cancer Supplement* October 15, 19971 Vol. 80, no. 8, pp. 1699-1701) *Body* 1999 *(‘A Dose Finding Study of Zoledronate in Hypercalcaemic Cancer Patients,’ Journal of Bone and Mineral Research* Vol. 14, no. 9, 1999, pp. 1557-l5561) (treatment of cancer-related bone disorder) — not zoledronic acid either. Buckler (‘*Single Infusion of Zoledronate in Paget’s Disease of Bone: A Placebo-Controlled, Dose-Ranging Study’, Bone,* Vol. 24, no 5 Supplement, May 1999: 815-855) pertains to the treatment of Paget’s disease, Sorbera describes clinical studies into the treatment of Paget’s disease and cancer-related bone disorders, and Wimalawansa (abstract, *Bone* S648, 1998) concerns one patient with sarcoidosis. Even apart from the fact that none of these publications suggests a dosing interval of one year, the skilled person knew on the priority date that the results obtained with a bisphosphonate for the treatment of the one indication could not just like that be extrapolated to the use of that bisphosphonate (let alone yet another bisphosphonate) for another indication. That is inter alia evident from Adami (‘*Duration of the effects of intravenous alendronate in postmenopausal women and in patients with primary hyperparathyroidism and Paget’s disease of bone,’ Bone and Mineral* 25 (1991,) 75-82), in which it is mentioned:

> *“Thus, the same dose of alendronate induces comparable fractional decreases of bone resorption in the three groups of patients, but the effect is persistent only in Paget‘s disease. (...). In osteoporotic and primary hyperparathyroid patients, as soon as the treatment is withdrawn, the appearance of new sites of resorption is not inhibited and bone turnover is resumed to pre-treatment values.”*

These publications do therefore not yield a pointer either that would bring the skilled person starting from WO 421 to the application of a dosing interval of one year.

4.24 The mere circumstance that it was known that zoledronate is a very potent bisphosphonate, would not induce the skilled person either. The potency of a bisphosphonate did give a person with average skill in the art an indication on the dosing quantity on the priority date, namely the more potent a bisphosphonate, the less needed to have an effect. This did however not hold true for the dosing interval. On the priority date it was known that the potency of a bisphosphonate was exactly not indicative for the duration of effectiveness thereof. About the potent bisphosphonate risedronate it was known on the priority date that this exactly does not have a long duration of effectiveness in the treatment of osteoporosis and was therefore used for a 3 monthly interval (par. 115 of the first statement of Prof R.G.G. Russell, party expert on the part of Novartis, with reference to Mortensen (‘*Risedronate Increases Bone Mass in an Early Postmenopausal Population: Two Years of Treatment Plus One Year of Follow-Up,’ J. Clin. Endocrinol Metab* 83: 396-402, 1998)).

4.25 The total dose principle referred to by Sun would not bring the skilled person either without any inventive conceptual labour to a dosing interval of one year. In the handbook by Prof Papapoulos, (‘*The Aging Skeleton,*’ 1999), which must be considered to be part of the

common general knowledge of the art on the priority date, it is explained on p. 543 that it is not evident at all that this principle is applicable just like that to bisphosphonates and that this has not been sufficiently researched as yet in relation to the treatment of osteoporosis:

> *"An issue that can create some confusion among treating clinicians is the assumption that the total dose of bisphosphonate delivered to the skeleton will determine the final biological response. Studies in patients with high rates of bone turnover, such as Paget's disease, have shown that this is not true and that the magnitude of suppression of bone resorption depends largely on the amount of bisphosphonate presented to the bone surface al any particular time. 1f the same dose is divided over a long period, the final result will be different and the response will be incomplete. The possible implications of these pharmacodynamic principles have not yet been explored adequately in patients with osteopororis."*

4.26 Finally the Court of Appeal notes that in WO 421 only a very broad range of possible dosages is mentioned (0.25 mg — 255 mg, more in particular 0.75mg -180 mg starting from a body weight of 75 kg, p.7, 1st par.) with reference to what is common for the treatment of other bone disorders such as osteoporosis. How the skilled person starting from WO 421 would arrive without any inventive conceptual labour at the dosing of 2-10 mg for intravenous administration of zoledronic acid for the treatment of osteoporosis, has not been made sufficiently insightful by Sun. The mere argument that the skilled person would understand that the lower part of the dosing range would pertain to zoledronate and would routine-like design a clinical study and thus arrive at a suitable dosing range, does not suffice.

4.27 The conclusion is that the inventive step attack of Sun fails, just like for that matter in the English action.

Infringement

4.28 Since for the time being both novelty and inventive step of the patent must be assumed, the Court of Appeal has arrived at the question whether Sun commits (indirect) infringement of the patent.

4.29 Paget's disease is a very rare disorder whereas osteoporosis is a common disease, especially in women over 50 years of age. Also, for the treatment of Paget's disease usually only one administration is needed, whereas for the treatment of osteoporosis an administration interval of one year holds true. According to a substantiated estimation of Novartis – not sufficiently challenged by Sun as such with reasons – on the basis of the turnover of Aclasta in the years 2011-2013 (before a generic product was put in the market) it is to be expected that 97.3% of the medicine zoledronic acid 5mg/l00 ml will be used for the treatment of osteoporosis, the remaining 2.7% for the treatment of Paget's disease, or 135

units on the basis of an anticipated total turnover of 5,000 units per year.[6] The calculation of Sun that 17,500 people would qualify for the treatment of Paget's disease cannot detract from this, since this concerns a total number of people on the total population suffering from the disease, but that are usually all treated only once and of which a large part will have already been treated. The number calculated by Novartis of 135 units pertains to the anticipated number of patients that still need annual treatment. Whatever may be of the different calculations drawn up by parties and the exact outcome of the magnitude of the patient populations, it is plausible that Paget's disease occurs considerably less frequently and needs considerably less treatment than osteoporosis.

4.30 On the basis of the used preferential policy all patients that are insured with VGZ and that get zoledronic acid 5 mg/l00 ml prescribed for home treatment, irrespective of the indication, are/may only be supplied with the Generic Product.[7] Since it must be assumed that the group of people insured with VGZ is a representative reflection of the Dutch population, the conclusion is inevitable that the Generic Product will also, and even for the vast majority, be prescribed and supplied for the treatment of osteoporosis that has been put under protection by claim 7 of the patent.

4.31 It is not in dispute that the generic 5 mg/100 ml zoledronic acid offered and supplied by Sun to wholesalers (for sale to pharmacies) is an essential part of the invention in accordance with claim 7 of the patent.

4.32 Sun has unconditionally registered for the tender of VGZ for the supply of the Generic Product, irrespective of the indication that it would be used for, and committed itself to supply unlimited quantities of Generic Product. Its range was thus not limited to supply of the Generic Product for application in Paget's disease, but also extended to the use for the treatment of osteoporosis. The e-mail sent afterwards by Sun to VGZ, in which for the sake of clarity once again pointed out that the Generic Product is exclusively intended for the treatment of Paget's disease and that the indication osteoporosis is still protected by a patent of Novartis, is not prejudicial to this, since it does not connect any consequence to that communication in respect of the previously entered-into unconditional and unlimited commitment to supply.

4.33 Given the preference policy used by VGZ the conclusion is likewise inevitable that the Generic Product will also be supplied for the benefit of and used for the treatment of osteoporosis. As Sun recognizes, physicians usually only prescribe the active ingredient and pharmacists are moreover obliged to supply the designated preferential product, even if Aclasta is prescribed on its brand name (except for the negligible number of cases of medical necessity). In view of the ratio of the numbers of patients suffering from Paget's disease on

[6] Statement Prof Papapoulos, party expert on the part of Novartis, par. 40 ff.
[7] Apart from a number of cases, negligible in this respect, in which the patient may be supplied with Aclasta on the basis of a medical necessity, e.g. intolerance for one the excipients used by Sun in the Generic Product.

the one hand and those suffering from osteoporosis on the other hand, it is practically excluded that the Generic Product is not supplied and used for the latter disorder. Sun should know for that reason that its product would also be supplied for the patented indication at the end of the vertical supply chain. Likewise the sale of 142 units of the Generic Product on only the months of January and February 2014[8] makes that Sun had to realize that chances are very high that its products are supplied and used for the patented application. Even if Sun would be followed in its argument, which is not substantiated for that matter, that zoledronic acid 5 ml/100 ml would be prescribed more often now than before because currently a cheaper alternative is available, and also if the Generic Product would be exported, as Sun suggested, but also failed to substantiate. In the provisional opinion it has therefore been complied with the knowledge in Sun of infringing use of the Generic Product required for assuming indirect infringement.

4.34 Sun argued that it cannot be blamed for any of this because are the consequences of the preference policy used by VGZ and of the tender floated by VGZ that did not allowed conditional tendering (only for use in the Paget's disease indication). The Court of Appeal is provisionally of the opinion that this does not absolve Sun. Under the given circumstances, in which it was obvious to Sun beforehand that the conduct of VGZ would inevitably lead to the Generic Product also being used for osteoporosis and therefore for the indication protected by the patent, it was appropriate for Sun to do everything possible to prevent the Generic Product from being supplied for the treatment of osteoporosis, which would infringe the patent of Novartis. Sun failed in this.

4.35 After having been warned by Novartis, Sun sent an e-mail to the wholesalers (and pharmacists that directly order from same) with the following content:

> *Dear client,*
>
> *This announcement pertains to formality.*
>
> *Advised by our attorney we would like to point out to you that our product Zoledronic acid SUN 5 mg/100 ml, Z-index no. 15958264, commercialized by us, is currently only intended for the treatment of Paget's disease. This is also the indication that is mentioned in the patient information leaflet Zoledronic acid SUN 5 mg/100 ml. For the time being the indication osteoporosis has not been included since this indication is still protected by a patent of Novartis.*
> *By accepting the delivery of Zoledronic acid SUN 5mg/100 ml solution for infusion, you indicate to be aware to the above.*

Under the given circumstances that did not suffice. It should at least have made it clear (as well) that it was not allowed to prescribe and supply the Generic Product for the treatment of

[8] On the basis of information of Farminform, Exhibit 28 Novartis.

osteoporosis, because this would commit infringement of the patent rights of Novartis. It should have made sure that effective measures would be taken to ensure that this would not happen. By instead starting the e-mail with “This announcement only concerns a formality,” it created on the other hand the suggestion that no importance needed to be attached in practice to the fact that the Generic Product is only intended for the treatment of Paget’s disease and that the indication osteoporosis is still protected by a patent of Novartis, nor that this necessitated any measure.

4.36 Sun likewise failed to furnish sufficient substantiation that it made an effort to convince VGZ that it should frame its tender differently to enable Sun to tender with due respect for the patent rights of Novartis, for instance by separating the tender for zoledronic acid for the application to osteoporosis on the one hand and for the application to Paget on the other hand. If VGZ would not (have) be(en) sensitive to that argument and the design of the tender would make it impossible for Sun to tender, this is a circumstance that Sun must hold against VGZ. This does however not absolve Sun to commit infringement of the patent rights of Novartis.

4.37 The conclusion is that the Court of Appeal is provisionally of the opinion that Sun commits indirect infringement of the Patent within the meaning of art. 73 jo.70 ROW ([Dutch] National Patent Act, “ROW”).

The claims

4.38 The indirect infringement injunction claimed by Novartis qualifies for allowance. The position of Sun that such injunction would be in breach of Dutch or European law of competition is rejected. It must be put first and foremost that the liberty of Sun to offer and supply its Generic Product for the treatment of treatment of Paget’s disease is not affected by the injunction applied for by Novartis to commit indirect infringement of its patent. That such injunction would lead in practice to hampering the supply of the Generic Product for the treatment of Paget’s disease results from VGZ’s manner of compensation of medicinal products to its insurants — as long as VGZ still opts for applying its currently prevailing preference policy without any concession — and is limited to the insurants of VGZ. This is not a circumstance that Novartis has any influence on or that can be imputed to same. Imposing a general injunction to commit indirect infringement can moreover not be qualified as an arrangement that is inadmissible in terms of competition law, but as the enforcement of a legal monopoly by Novartis on the basis of the patent rights allowed to same. That Novartis would abuse a position of power by enforcing its patent rights against Sun has not been sufficiently substantiated with reasons by Sun.

4.39 The argument of Sun moreover that imposing a general injunction to commit indirect infringement could possibly lead to enforcement issues does not create sufficient cause to refrain from this, given the justified interest of Novartis to act against indirect infringement of its patent rights.

4.40 The circumstance that Novartis could possibly also take action against third parties on the basis of direct infringement or unlawful act, as also argued by Sun, is not prejudicial to Novartis not only having the right, but also a justified interest to take action against Sun on the basis of indirect infringement. With this it can effectively combat infringing conduct further on in the distribution channel – and thus further harm. The argument of Sun that Novartis would first (or only) have to take action against all individual direct infringers in order to limit its damage cannot be accepted as correct.

4.41 The injunction also claimed by Novartis to participate in tenders and/or enter into agreements for the supply of the Generic Product if not exclusively limited to the treatment of Paget's disease, is denied because Novartis does not have an individual interest in this. It follows from the reasons given herein above that under circumstances – more in particular if no effective measures are taken as well to ensure that further on in the distribution channel no infringement is committed of the patent rights of Novartis - under circumstances – more in particular if no effective measures are taken as well to ensure that further on in the distribution channel no infringement is committed of the patent rights of Novartis - such conduct of Sun can be designated as indirect infringement. A general indirect infringement injunction therefore suffices.

4.42 The Court of Appeal fails to see any cause for the order claimed by Novartis to keep administration of the Generic Product still to be sold and to render accountability thereof in addition to the general indirect infringement injunction.

4.43 The claimed order to send a letter to the healthcare insurers and hospitals that have floated a tender or with whom an agreement has been concluded for the supply of Generic Product, shall be allowed in the form as formulated herein below. In an order to send a letter to those that still want to organize a tender or want to conclude an agreement Novartis does not have any interest in view of the allowance of the general indirect infringement injunction, for the same reasons as elaborated herein above in reason for the decision 4.41.

4.44 The Court of Appeal shall mitigate the claimed penalties to an amount of € 5,000.- per product with which, and € 50,000.- per day (or part thereof), infringement is made and maximize this to an amount of € 5,000,000.-. The Court of Appeal does not see any cause for the extension of 14 days as requested by Sun to enable the latter to export its stock since Sun retains the freedom to commercialize its Generic Product in a non-infringing manner and export moreover does not constitute any indirect infringement in The Netherlands.

Legal costs

4.45 As the party found against Sun must be sentenced in the legal costs of Novartis in both instances. The legal costs specified by Novartis are not challenged by Sun so that these can be allowed as claimed, to wit € 180,064.48 to be increased with the court fee in the

amount of €608,- in first instance and € 183,397.98 (including service costs) to be increased with the court fee in the amount of € 704,- on appeal, therefore in total an amount of € 364.774.46.

Decision

The Court of Appeal:

5.1 sets aside the judgment an appeal and giving a new judgment:

5.2 forbids Sun with immediate effect after service of this ruling to commit indirect Infringement of (the Dutch part of) EP 1 296 689 on pain of penalty of an immediately exigible penalty of € 50,000.- for each and every day or part thereof that Sun breaches this injunction, or – all of this at the discretion of Novartis – of € 5,000.- per product with which this injunction is violated, all of this up to a maximum of € 5,000,000.-:

5.3 sentences Sun within 2 business days after service of this ruling to inform in writing all insurance companies and hospitals that have floated a tender in which Sun has participated and all parties that have concluded an agreement with Sun with regard to zoledronic acid 5 mg/100 ml in The Netherlands with exclusively the following text (that is, without additional text or cover letter):

> *Dear [name contact person, insurance company/hospital]*
>
> *By ruling of 27 January 2015 the Court of Appeal The Hague ruled in summary proceedings that by supplying or offering Zoledronic acid SUN 5mg solution for infusion we commit indirect infringement of the patent rights of Novartis. Insofar as the tender procedure/agreement that you have initiated/concluded with us comprises the indication osteoporosis, we inform you that we are not (any longer) able to participate/supply. We can exclusively participate in a tender procedure/agreement with sufficient guarantees that the supply of 5 mg/100 ml zoledronic acid for the treatment of osteoporosis is prevented.*

5.4 sentences Sun to pay the legal costs on the part of Novartis in both instance, estimated to amount to € 364,774.46;

5.5 declares this ruling as much as possible provisionally enforceable.

This ruling is given by *Mr* R. Kalden, *Mr* E.F. Brinkman and *Mr* C.J.J.C. van Nispen and was pronounced in open session of 27 January 2015 in the presence of the Clerk of the Court.