ruling

COURT OF APPEAL OF THE HAGUE

Civil Law Section

Case number : 200.174.337/01

Case number District Court : C/09/468395 / HA ZA 14-738

ruling of 16 February 2016

in the matter of

1. the private company with limited liability
ASTRAZENECA B.V.,
with registered office in Zoetermeer,
2. the legal entity organized under foreign law
SHIONOGI SEIYAKU KABUSHIKI KAISHA,
established in Osaka, Japan,
appellants in the appeal on the main issue,
respondents in the cross appeal,
hereinafter referred to individually as Astrazeneca B.V. and Shionogi and collectively as Astrazeneca (in the singular),
attorney: L.Ph.J. baron van Utenhove, LL.M. of The Hague,

versus

the legal entity organized under foreign law
RESOLUTION CHEMICALS LIMITED,
established in Stevenage, United Kingdom,
respondent in the appeal on the main issue,
appellant in the cross appeal,
hereinafter referred to as: Resolution,
attorney: D. Knottenbelt, LL.M. of Rotterdam.

1. The proceedings

By virtue of a writ dated 27 July 2015 with exhibits, also containing 8 grounds for appeal, Astrazeneca lodged an appeal against the judgment dated 15 July 2015 that the District Court of The Hague rendered between the parties (hereinafter also: the judgment). On 4 August 2015, Astrazeneca filed a motion for injunctive relief by virtue of Section 223 DCCP, also containing document for submitting exhibits. Subsequently, Astrazeneca withdrew its claim in the motion. By virtue of a statement of defence in the appeal on the main issue, also statement of cross appeal with exhibits, Resolution challenged Astrazeneca's grounds for appeal and advanced two grounds for appeal in the cross appeal. Subsequently, by virtue of a statement of defence in the cross appeal, Astrazeneca challenged Resolutions grounds for appeal in the cross appeal. After this, both parties also submitted additional exhibits by virtue of a document. Subsequently, on 12 November 2015, the parties had the case argued by their attorneys: Astrazeneca by W.A. Hoyng, LL.M. and J.M.J.A.

Krens, LL.M., attorneys in Amsterdam, assisted by patent attorney Dr J.H.J. den Hartog; Resolution by M.G.R. van Gardingen, LL.M. and H.J. Pot, LL.M., attorneys in Amsterdam, assisted by patent attorney Drs K.L.M. Bijvank, on both sides based on written pleadings that were submitted. Finally, the parties requested that the Court of Appeal render a ruling.

2. Facts

The facts established in the challenged judgment are not in dispute. The Court of Appeal will also start from these facts.

The case at issue involves the following:

2.1 Resolution's business is the development and production of active pharmaceutical ingredients.

2.2 Shionogi is a Japanese pharmaceutical company that is the holder of the supplementary protection certificate 300125 (hereinafter also: the SPC) for the Netherlands that has been granted for the product '*Rosuvastatinum, if required in the form of a non-toxic pharmaceutically acceptable salt, in particular calcium salt*'. The SPC, which is based on European patent 0 521 471 (hereinafter: EP 471 or the (basic) patent), has been exclusively licensed to Astrazeneca B.V. In the Netherlands, Astrazeneca B.V. markets rosuvastatin calcium under the brand name Crestor®. Astrazeneca B.V. is also the holder of the marketing authorization for Crestor® in the Netherlands. The SPC expires on 29 June 2017, unless the application for paediatric extension of the SPC is granted. In that case, the duration of the SPC will be extended to 29 December 2017.

2.3 Shionogi was the holder of EP 471, which pertains to '*Pyrimidine derivatives as HMG-CoA reductase inhibitors*' (in the unchallenged Dutch translation: '*Pyrimidinederivaten als HMG-CoA-reductase-inhibitoren*'). The patent was granted on 25 October 2000 by virtue of a patent application dated 30 June 1992, invoking priority of 1 July 1991 based on JP 18801591. The patent, which expired on 29 June 2012, was designated for the Netherlands, amongst other countries. No opposition was brought against the grant of the patent.

2.4 The patent has 16 claims. Claim 1 pertains to the compound rosuvastatin acid or a non-toxic pharmaceutical salt thereof.

2.5 The (authentic) English text of claim 1 reads as follows:

> 1. The compound (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid or a non-toxic pharmaceutically acceptable salt thereof.

2.6 The undisputed Dutch translation of claim 1 of EP 471 reads as follows:

> 1. Verbinding (+)-7-[4-(4-fluorfenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxi-(E)-6-hepteenzuur of een niet-toxisch farmaceutisch aanvaardbaar zout daarvan.

2.7 The description of EP 471 *inter alia* contains the following passages:

[0001] The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

[0002] The first generation of drags [bedoeld zal zijn: drugs, hof] for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, are mevinolin (...), pravastatin sodium (...), and simvastatin (...), which are fungal metabolites or chemical derivatives thereof. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (...) were developed as the second generation drags [idem, hof].

[0003] The compounds of the present invention inhibit the HMG-CoA reductase, which plays a major role in the synthesis of cholesterol, and thus they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

(...)

[0006] In the specification, the term "lower alkyl" refers to a straight, branched, or cyclic C_1 to C_6 alkyl, including methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, cyclopentyl, n-hexyl, and isohexyl and the like. Further, the lower alkyl may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano. Halogen means fluorine, chlorine, bromine and iodine.

[0007] The term "a non-toxic pharmaceutically acceptable salt" refers to a salt in which the cation is an alkali metal ion, an alkaline earth metal ion, or an ammonium ion. Examples of alkali metals are lithium, sodium, potassium, and cesium, and examples of alkaline earth metals are beryllium, magnesium, and calcium. Sodium and calcium are preferred.

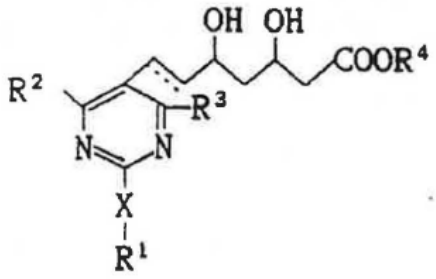
(...)

[0029] The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

(...)

2.8 Claim 1 as set forth in the original application of EP 471 reads as follows:

1. A compound represented by the formula (I):



(I)

wherein R^1 is lower alkyl, aryl of aralkyl, each of which may have one or more substituents; R^2 and R^3 each is independently hydrogen, lower alkyl or aryl, and each of said lower alkyl and aryl may have one or more substituents; R^4 is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone.

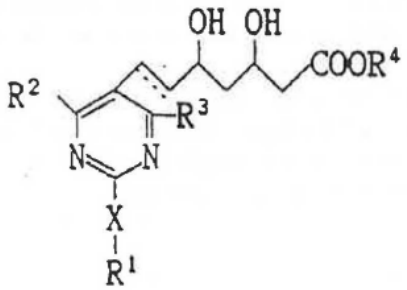
2.9 The description of the original application includes the following passages:

(page 2, lines 1 and 2)

The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

(page 2, lines 9-29)

The compounds of the present invention inhibit the HMG-CoA reductase, which plays a major role in the synthesis of cholesterol, and thus they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.
The present invention relates to compounds of the formula (I):



(I)

wherein R^1 is lower alkyl, aryl of aralkyl, each of which may have one or more substituents; R^2 and R^3 each is independently hydrogen, lower alkyl or aryl, and each of said lower alkyl and aryl may have one or more substituents; R^4 is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a substituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone. This invention also provides a pharmaceutical composition comprising the same.

(page 2, lines 42-45)

The term "a cation capable of forming a non-toxic pharmaceutically acceptable salt" refers to an alkali metal ion, an alkaline earth metal ion, or an ammonium ion. Examples of alkali metals are lithium, sodium, potassium, and cesium, and examples of alkaline earth metals are beryllium, magnesium, and calcium. Sodium and calcium are preferred.

(page 4, lines 29 and 30)

The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

(page 8, lines 43-47)

Example 1

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ia-1)

[...]

(page 13, lines 16-58 and page 14, lines 1-22)

Example 7

Calcium salt of the compound (I^{a-1})

The compound (I^{a-1}) (sodium salt) 1.50 g (3.00 mmol) is dissolved in 15 ml of water and stirred at room temperature under a nitrogen atmosphere. Successively 3.00 ml (3.00 mmol) of 1 mol/L calcium chloride 3.00 ml (3.00 mmol) is added dropwise thereto over 3 minutes. The reaction mixture is stirred at the same temperature for 2 hours, and the resulting precipitate is collected, washed with water and dried to give 1.32 g of calcium salt as powder. This compound started to melt at a temperature of 155 ° C, but the definitive melting point is ambiguous. [α]D = +6.3±0.2° (C = 2.011, 25.0 ° C, MeOH)

Anal Calcd. (%) for $C_{22}H_{27}N_3O_4SF \cdot 0.5Ca \cdot 0.5H_2O$					
:	C,51.85;	H,5.53;	N,8.25;	F,3.73;	Ca,3.93
Found :	C,51.65;	H,5.51;	N,8.47;	F,3.74;	Ca,4.07

Biological Activity
Experiment

The HMG-CoA reductase inhibitory effect

(1) Preparation of rat liver microsomes

Sprague-Dawley rats, which were in free access to ordinary dietes containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsomes. The thus obtained microsomes were then purified according to the manner described by Kuroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105000 x g was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down and kept at -80 ° C.

(2) Measurement of the HMG-CoA reductase inhibitory activities

The rat liver microsome sample (100 μ l), which was preserved at -80 ° C, was fused at 0 ° C and diluted with 0.7 ml of a cold potassium phosphate buffer (100 mM pH7.4). This was mixed with 0.8 ml of 50 mM EDTA (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100 mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the

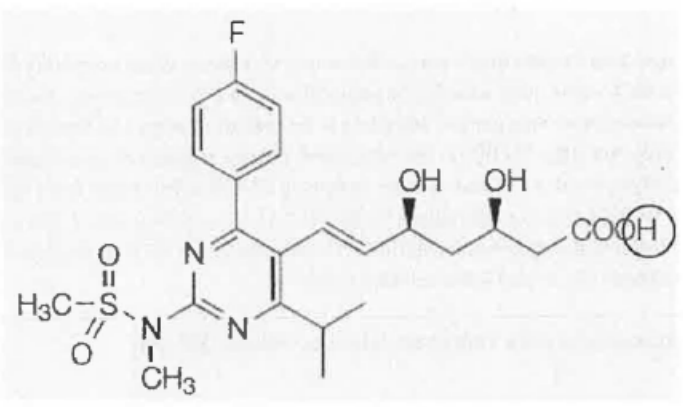
mixture was kept at 0 ° C. The microsome solution (1.675 ml) was mixed with 670 µ l of 25 mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to the solution of 0.5mM [3-^{14}C]HMG-CoA (3mCi/mmol). A solution (5 µ l) of sodium salt of the test compound dissolved in potassium phosphate buffer was added to 45 µ l of the mixture. The resulting mixture was incubated at 37 ° C for 30 minutes and cooled. After termination of the reaction by addition of 10 µ l of 2N-HCL, the mixture was incubated again at 37 ° C for 15 minutes and then 30 µ l of this mixture was applied to thin-layer chromatography on silica gel of 0.5 mm in thickness (Merck AG, Art 5744). The chromatograms were developed in toluene/acetone (1/1) and the spot, whose Rf value was between 0.45 to 0.60, were scraped. The obtained products were put into a vial containing 10 ml of scintillator to measure specific radio-activity with a scintillation counter. The activities of the present compounds are shown in Table 4 as comparative data, based on the assumption that the activity of mevinolin (sodium salt) as the reference drug is 100.

Table 4

Test Compound	HMG-CoA reductase inhibitory activities
I a-I	442
I a-3	385
I a-5	279
I a-7	260
Mevinolin Na	100

The test data demonstrates that the compounds of the present invention exhibit HMG-CoA reductase inhibition activities superior to mevinolin.

2.10 In contrast to the original application, which claimed a class of compounds by means of a Markush formula, EP 471 only pertains to rosuvastatin. EP 471 claims the acid of rosuvastatin; see the structural formula below (which has been derived from the statement by Professor Dr J.W. Jukema that Astrazeneca submitted as Exhibit GP3). In that case, the R^4 group represented in claim 1 of the original application (see 2.8) is H, circled in red below. Choices are also made for the R^1, R^2, R^3 and X groups.



2.11 EP 471 also claims non-toxic pharmaceutical salts of rosuvastatin, including the sodium salt and the calcium salt. In these salts of rosuvastatin, the R^4 position is sodium (Na) and calcium (Ca), respectively. The rosuvastatin anion is not claimed in EP 471.

2.12 Resolution obtained a marketing authorization for the marketing of rosuvastatin zinc and intends to put that product on the market in the Netherlands. Resolution notified Shionogi et al. of this in a letter dated 26 March 2014. On 4 April 2014, attorney Hoyng informed Resolution on Shionogi et al.'s behalf that Shionogi et al. are not prepared to confirm that they will not invoke SPC 300125 against Resolution, its buyers and their buyers if they start selling rosuvastatin zinc on the Dutch market.

3. The technical background

The explanation of the technical background of the patent below has been derived from the undisputed explanation in the challenged judgment.

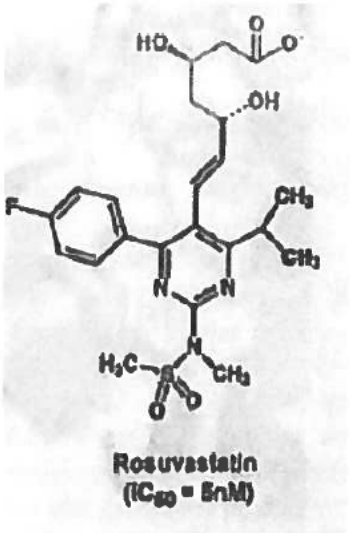
3.1 Cholesterol is a fatty substance that the human body primarily uses as a building block for cell membranes and to produce bile acid. Given that cholesterol is insoluble, the blood transports it as a complex in specific, various types of proteins. Two main types of cholesterol are distinguished: LDL cholesterol (LDL means 'low density lipoprotein') and HDL cholesterol (HDL means 'high density lipoprotein). However, these are the same cholesterol, but 'packaged' in different proteins.

3.2 LDL and HDL perform different functions. LDL transports cholesterol from the liver through the body, while HDL returns (an excess of) cholesterol to the liver, where it can be broken down and further eliminated. If the LDL cholesterol content in the blood is relatively high, it will stick to the inside of the arteries. This is especially true if the cholesterol is oxidized. As a result, the arteries get clogged, which increases the risk of cardiovascular disorders, such as heart attacks and strokes. HDL does not have such effects.

3.3 Approximately 1/3 of the cholesterol that is present in the human body has been consumed. The other 2/3 is primarily produced in the liver. The cholesterol that is produced in the liver is transported primarily in LDL 'packets'. The biological process of the production of cholesterol is very complex; this involves a large number of steps, including several enzymatic conversions.

3.4 The rate-limiting step in the production of cholesterol is the conversion of HMG-CoA to mevalonate by the HMG-CoA reductase enzyme. Statins (also called HMG-CoA reductase inhibitors) are a class of medicinal products that are used to reduce the cholesterol levels (as LDL complex) by inhibiting the HMG-CoA reductase enzyme, which plays a central role in the production of cholesterol in the liver. Reducing the production of cholesterol in the liver also inhibits the amount of LDL cholesterol that is transported through the body in the blood.

3.5 One of the statins referred to above is rosuvastatin. The pharmaceutically active form is the rosuvastatin anion, a negatively-charged ion. This anion binds to the HMG-CoA reductase enzyme. If HMG-CoA reductase binds to the rosuvastatin anion rather than to HMG-CoA, the reductase is blocked (inhibited), as a result of which the production of cholesterol in the liver is inhibited. The structural formula of the rosuvastatin anion is depicted below:



3.6 Only the anion is responsible for the biological activity of rosuvastatin, namely the HGM-CoA reductase inhibiting effect. It is not possible to make a tablet in which the active ingredient is the anion; only neutral substances can be used. This implies the presence of a cation (a positively-charged particle with which rosuvastatin salt is formed) or hydrogen (with which rosuvastatin acid is formed).

3.7 The salt form of rosuvastatin influences the practical suitability of the medicinal product, because the salt form is relevant, for example, for the solubility and the chemical and storage capacity. The suitability of the salt form is determined by salt screening.

4. The dispute in the first instance and on appeal

4.1 In the first instance, Resolution moved – summarized – that in a judgment that is declared provisionally enforceable to the extent possible, the District Court nullifies claims 1 and 2 of the Dutch part of EP 471 and the dependent claims, and further nullifies SPC 300125 to the extent that the subject matter of this SPC pertains to a compound other than rosuvastatin calcium and/or rosuvastatin sodium, as well as renders a declaratory judgment to the effect that Resolution (and/or its customers) does not/do not infringe Astrazeneca's rights under SPC 300125, either directly or indirectly, by marketing rosuvastatin zinc in the Netherlands, with a joint and several order for Astrazeneca to pay the costs of the proceedings, to be estimated by virtue of Section 1019h DCCP, plus the statutory interest.

4.2 To this end – in brief – Resolution contended that claims 1 and 2 of the Dutch part of EP 471 as well as the dependant claims should not have been granted on account of added subject matter to the extent that these comprise more than rosuvastatin calcium and/or rosuvastatin sodium, as well as that with the intended marketing of rosuvastatin zinc in the Netherlands – including if the SPC is deemed to be (fully) valid – Resolution will not infringe the SPC, because rosuvastatin zinc is not covered by the extent of the protection that is conferred by the SPC.

4.3 The District Court nullified the SPC to the extent that the protection it confers extends to products other than the non-toxic pharmaceutically acceptable salts of rosuvastatin in which the cation comprises an alkali metal ion, an alkaline earth metal ion, or an ammonium anion.

4.4 To this end, briefly summarized and in as far as currently relevant, the District Court held that in light of paragraph 7 of the description, the feature "*a non-toxic pharmaceutically acceptable salt thereof*" mentioned in claim 1 of EP 471 must be taken to mean a salt in which the cation comprises an alkali metal ion, an alkaline earth metal ion, or an ammonium anion, so that the extent of the protection that is conferred by the patent is limited to this (judgment, par. 4.13 – 4.20). The District Court further held that rosuvastatin salts other than the calcium or sodium salt do not constitute added subject matter, while the rosuvastatin acid does (judgment, par. 4.21 – 4.29).

4.5 Astrazeneca directed grounds for appeal against the District Court's finding that the average skilled person would take paragraph 7 of the patent's description to be a limiting definition and understand that the patent proprietor only wanted to confer protection for the salts mentioned in this paragraph for use with rosuvastatin (judgment, par. 4.16) and the rejection of Astrazeneca's point of view that this paragraph 7 would only be regarded as a non-exhaustive list (judgment, par. 4.17 – 4.19). Astrazeneca further (*inter alia*) directed a ground for appeal against the District Court's finding (judgment, par. 4.28) that the claimed acid of rosuvastatin constitutes added subject matter.

4.6 In its cross appeal, Resolution *inter alia* challenges par. 4.10 of the judgment, in which the facts regarding salt screening are allegedly established in a too limited manner and further against the District Court's finding (judgment, par. 4.21 – 4.27) that claiming salts of rosuvastatin other than the calcium or sodium salt does not constitute added subject matter.

5. Assessment

<u>In the appeal on the main issue</u>

5.1 The question to be answered is how the claim feature '*or a non-toxic pharmaceutically acceptable salt thereof*' in claim 1 of EP 471 must be interpreted. Resolution's point of view that Astrazeneca did not direct any ground for appeal against par. 4.17 of the judgment and that it is an established fact between the parties that paragraph 7 of the description offers a definition in the form of an exhaustive list is rejected. Ground for Appeal II of Astrazeneca, read in conjunction with paragraphs 35-39 of the notice of appeal, comprises that Astrazeneca also complained about the District Court's rejection of its argument that the average skilled person will take paragraph 7 of the description to be a non-exhaustive list.

5.2 With regard to the interpretation of a patent claim, the Supreme Court *inter alia* found as follows in the *Medinol / Abbott* ruling (HR 4 April 2014, ECLI:NL:HR:2014:816) (in par. 3.4.2):

> *Article 69 (1) of the European Patent Convention (EPC) comprises that the extent of the protection that is conferred by a patent is determined by the claims of the patent specification, in which the description and drawings serve to interpret those claims. Article 1 of the protocol on the interpretation of Article 69 EPC (hereinafter: the Protocol) reads:* "Article 69 should not be interpreted as meaning that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, in which the description and drawings are only employed for the purpose of resolving an ambiguity found in the claims. Nor should it be taken to mean that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patent proprietor has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patent proprietor with a reasonable degree of legal certainty for third parties." *In accordance with this interpretation rule of the Protocol, the Supreme Court labelled the formulations used in its preceding rulings,* "which is essential for the invention whose protection is invoked", and "the inventive idea underlying the words of those claims" *as a point of view, as opposed to the literal text of the claims (the "extremes" in the words of the Protocol) (cf. HR 7 September 2007, ECLI:NL:HR:2007:BA3522, NJ 2007/466 and HR 25 May 2012, ECLI:NL:HR:2012:BV3680, NJ 2013/68). In this context, establishing the inventive idea underlying the words of the claims serves to avoid an interpretation that is based exclusively on the literal meaning of the wording and therefore may possibly be too limited or unnecessarily broad for a reasonable protection of the patent proprietor (cf. HR 13 January 1995, ECLI:NL:HR:1995:ZC1609, NJ 1995/391). In this framework, the description and drawings constitute an important source. The description includes an overview of the prior art that the applicant considers useful for understanding the invention (Rule 42 of the Implementing Regulations to the EPC). Prior art that is not mentioned in the description may also be relevant. After all, the guiding principle in interpreting a patent is the perspective of the average skilled person with his knowledge of the prior art.*

The inventive idea underlying the words of the claims

5.3 The issue in identifying the inventive idea is establishing what the patent adds to the prior art; the perspective of the average skilled person and his knowledge of the prior art on the priority date is the guiding principle in this (cf. HR in *Medinol / Abbott*, par. 3.5.2). In addition, the description and drawings constitute an important source in establishing the inventive idea (cf. HR in *Medinol / Abbott*, par. 3.4.2 cited above). It is not in dispute that in the case at issue, the average skilled person is an organic chemist who is active in the development of new medicinal products, who in any event has basic knowledge of the activity of the medicinal products on the market, such as rosuvastatin.

5.4 Resolution's point of view (on the occasion of the pleadings on appeal) that the inventive idea lies in finding specific precursors (i.e. a number of specific salts of rosuvastatin) that after ingestion release the active ingredient that has an HMG-CoA reductase inhibitory effect is dismissed. Resolution bases its point of view on paragraph 7 of the patent. In so doing, Resolution fails to recognize that even though the description is an important source for identifying the inventive idea, the perspective of the average skilled person and his general professional knowledge on the priority date must also be taken into account (as a guiding principle).

5.5 The average skilled person reads in the description (paragraphs 1-3) that first-generation (fungal metabolites) and second-generation (synthetic) inhibitors of HMG-CoA reductase (also referred to as statins) had already been developed and that the patent discovered a new group of statins, namely 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Paragraph 4 of the description specifically mentions the acid or salt form of rosuvastatin that falls into this group, while it is further explained (in paragraph 5) that the invention also pertains to pharmaceutical compositions comprising the same and the process for preparing the same. Paragraphs 6 and 7 address the terms "lower alkyl group" and "a non-toxic pharmaceutically acceptable salt". The subsequent paragraphs (8-26) describe the process for preparing the new statins. Paragraphs 26-28 mention possible pharmaceutical compositions, along with how these can be prepared in the usual way as well as possible dosages. This is followed by reference examples in which processes for preparing a few compounds are set out, examples in which sodium and calcium salts of rosuvastatin are prepared and finally an experiment measuring the biological activity (the HMG-CoA reductase inhibitory effect). In the final paragraph 51 it is noted that the test data demonstrate that the compounds according to the invention – according to the table, this specifically refers to rosuvastatin – exhibit HMG-CoA inhibitory activity superior to mevinolin (a first-generation statin mentioned in paragraph 2 of the description).

5.6 In view of the description considered as a whole, taking into account his general professional knowledge on the priority date, the average skilled person will understand that the invention pertains to a new group of statins – in particular the specifically claimed rosuvastatin – whose biological activity is superior to a known first generation of statins. The novelty and inventive step of rosuvastatin has not been challenged. Thus, starting from the perspective of the average skilled person on the priority date, the patent adds a new group of statins to the known prior art, including – more specifically – rosuvastatin. The discovery of this qualifies as the inventive idea underlying the words of the claim(s).

5.7 The average skilled person does not find any indication in the description that (the most) suitable salts of this new group of statins and/or of rosuvastatin were searched for in particular. He does not infer this from paragraph 7 of the description or the examples. On the priority date – at which time first-generation and second-generation statins were already on the market – it was part of the average skilled person's general professional knowledge that the anion is the active ingredient of the statins (as Resolution acknowledged in point 36 of its written pleadings on appeal), but that this had to be administered in the acid or salt form, because it is not possible to produce a tablet with an anion (see par. 3.6 above). The salts mentioned in paragraph 7 of the description involve salts that – on the

priority date – were used to prepare the tablet form of already known statins (which did not include zinc) for administration. For that reason, the average skilled person understands from that paragraph that these are salts that may be expected to be suitable for preparing a tablet form containing a new statin according to the invention, whereby after intake into the body and dissolution of the salt, the pharmaceutically active anions are formed. The two examples included in the description only describe the process for preparing two salt forms of rosuvastatin, without comparing these forms or subjecting them to further tests. Subsequently, the experiment was only performed with the sodium salt; the biological activity was not compared with the calcium (or other) salt, but with another statin known from the prior art.

5.8 The above means that the notion that finding a suitable precursor (salt form) is the inventive idea underlying the wording of the claim(s) cannot be accepted as correct.

5.9 The fact that claim 1 of EP 471 only mentions rosuvastatin acid or a non-toxic pharmaceutically acceptable salt does not lead to any other opinion, either. As found before, in determining the inventive idea, the guiding principle is formed by what is added to the prior art viewed from the perspective of the average skilled person and not by the (literal) wording of the claim(s). After all, the inventive idea serves as the point of view in interpreting the claim(s).

Interpretation of 'or a non-toxic pharmaceutically acceptable salt thereof'

5.10 Claim 1 of EP 471 does not claim the active ingredient of rosuvastatin, the rosuvastatin anion, but rosuvastatin acid or a non-toxic pharmaceutically acceptable salt thereof. The parties disagree in particular regarding the interpretation of the feature 'or a non-toxic pharmaceutically acceptable salt thereof'. Resolution takes the position that in light of paragraph 7 of the description, this feature must be interpreted such that 'salt' only comprises one of the salts mentioned in paragraph 7. This means that according to Resolution, claim 1 must be interpreted more strictly than the literal wording of this claim give rise to. Astrazeneca takes the position that the average skilled person, taking into account his general professional knowledge on the priority date, would take paragraph 7 of the description to mean a non-exhaustive list and that there is no reason to interpret claim 1 more strictly than its literal meaning.

5.11 The Court of Appeal does not accept as correct that if and as soon as a patent contains a further description of a term used in a patent claim, this must always be taken to be restrictive, as Resolution appears to assume. Although this further description must be taken into account as part of the description in interpreting the patent claim, this is without prejudice to the fact that the question regarding whether such description must be taken to be restrictive depends on the question of how the average skilled person would understand this further description, taking into account the description and his general professional knowledge on the priority date. Just as the literal meaning of the words of the claim may not simply be started from in interpreting this claim, the literal text of a passage from that description may not simply be started from in interpreting this claim in light of the description. A passage from the description that is relevant for the interpretation of a claim must likewise be interpreted in the context of the entire description and from the perspective of the average

skilled person with his general professional knowledge on the priority date. Only if the average skilled person takes a further description (or 'definition') to be an exhaustive list, is this a decisive factor for the meaning of the feature of the claim to which this further description or definition pertains.

5.12 The Court of Appeal believes that in par. 4.18 of the judgment, with reference to the *AGA / Occlutech* ruling (HR 25 May 2012, ECLI:NL:HR:2012:BV3680), the District Court rightly held first and foremost that the average skilled person may only assume that part of the protection to which the patent confers entitlement has been waived in the event that there are valid reasons to do so in view of the content of the patent specification in light of possible other information, including the public information from the prosecution file. It follows from the preceding paragraph (par. 5.11) that the mere fact that the description contains a further description of a claim feature is insufficient to assume such valid grounds on this basis alone. Whether or not this is the case will depend on the answer to the question regarding how the average skilled person would construe this further description, in particular whether or not he would take this to be an exhaustive list.

5.13 Based on the findings below, in contrast to the District Court, the Court of Appeal finds that on the priority date, the average skilled person did not have valid reasons to assume that the patent proprietor only wanted protection for the salts of rosuvastatin mentioned in paragraph 7 and waived the broader protection that claim 1 offered according to its literal wording.

5.14 In interpreting a claim in light of the description, the inventive idea underlying the words of the claim must be taken into account as a point of view. As found before, this inventive idea can be formulated as finding a new group of statins, specifically including rosuvastatin, with an HMG-CoA reductase inhibitory effect. The average skilled person will realize that claim 1 is formulated in a more limited manner than the inventive idea gives rise to, namely the claim only confers protection for the rosuvastatin acid and the pharmaceutically acceptable non-toxic rosuvastatin salts thereof. He will explain this by the fact that it is not possible to administer the active ingredient (the rosuvastatin anion), so that rosuvastatin in the possible administration forms is claimed for this reason. The – broader – inventive idea does not give the average skilled person any reason to assume that the patent proprietor only wanted the patent to confer protection for specific salt forms and to waive all other salt forms. After all, as the average skilled person knows on the priority date, the salt form in which statins are administered is irrelevant for their biological activity, because the anion of the statin is the active ingredient and the salt only serves to administer the rosuvastatin anion in tablet form.

5.15 To the extent that Resolution intended to contend that according to the Protocol, the claims must be interpreted in light of the description, so that there is no room for taking the inventive idea underlying the words of the claim into account, or at least that the wording of the description must prevail, this point of view is dismissed. After all, an interpretation of the patent claims in light of the description must always start from the perspective of the average skilled person on the priority date, taking into account his general professional knowledge. This perspective is in part determined by the inventive idea.

5.16 Where Resolution pointed out that the inventive idea is just one of the points of view that must be taken into account in interpreting a patent claim, this is correct; however, this cannot help Resolution. After all, the other points of view mentioned by the Supreme Court do not point in another direction.

5.17 One of the other points of view pertains to the extent to which the invention brought innovation (see also par. 3.3.1 of HR 13 January 1995 in *Ciba Geigy / Oté Optics*, ECLI:NL:HR:1995:ZC1609). As Astrazeneca advanced and as not contested based on a sufficient substantiation, rosuvastatin is a very potent statin that is still the market leader, despite the presence of various (cheaper) generic statins.

5.18 Another point of view to be taken into account pertains to the nature of the patent; this also points in the direction of a broader extent of protection here than Resolution suggests. The patent is not a formulation patent disclosing a new administration form of a known substance, in which the extent of the protection is limited to this administration form alone. EP 471 discloses a new group of pharmaceutically active substances, of which claim 1 more specifically claims the new and inventive substance rosuvastatin; thus, this is a 'substance patent' for which absolute substance protection can be obtained and is generally also envisaged by the patent proprietor.

5.19 Nor does the description lead the average skilled person to realize that claim 1 must be interpreted more strictly than the literal words of this claim give rise to. As already found before (see par. 5.7), on the priority date, the average skilled person would realize that paragraph 7 of the description mentions salts that have been used to prepare the tablet form for administration of known statins; for that reason, he would understand that these are salts that may be expected to be suitable for preparing a tablet form containing a new statin according to the invention, in which the biologically active anions are formed after ingestion in the body. The patent specification does not offer the average skilled person any reason to assume that the list of salts provided in paragraph 7 was based on a salt screening. Only two salts are prepared in the examples, while the experiment does not compare different salt forms, but only compares the efficacy of a statin according to the invention against a statin according to the prior art. For the rest, the description does not offer any indication for the idea that the patent proprietor found that specific salts (let alone all salts except those mentioned in paragraph 7) are unsuitable for use with rosuvastatin, either.

5.20 Nor does the general professional knowledge of the average skilled person lead the average skilled person to assume that the list of salts in paragraph 7 is meant to be exhaustive. The average skilled person knew that it was common practice on the priority date to conduct a salt screening for pharmaceutical preparations that are (or must be) administered in the salt form, such as statins. After all, the selected salt may, for example, influence the chemical stability, storage stability and solubility of the pharmaceutical preparation. However, as Astrazeneca contended with reference to various statements by experts testifying on its behalf (Dr P.L. Spargo, 3rd statement, par. 13-16; Professor Dr H.W. Frijlink, par. 14-18 with reference to J.I. Wells, Pharmaceutical preformulation, 1988; N. Taylor, par. 10, 32-34; Dr L.E.C. Baert, par. 13-20; Dr M. Hoffmann, par. 16-21 and Dr J.G. Fokkens, par. 15-17), the average skilled person also knows that – especially at the stage in which a patent application must be drawn up and filed under time pressure and only a limited amount of the discovered

substance is usually available – it was not customary to conduct an exhaustive salt screening. This was limited to a number of salts (generally including sodium as the salt that was by far the most commonly used, followed by calcium and potassium) and was only expanded to include other salts if there was a reason to do so. Resolution did not advance a sufficiently substantiated challenge to this. The publication by Morris et al. that Resolution cited (*An integrated approach to the selection of optimal salt form for a new drug candidate*, 1994 (dating from after the priority date)) does not present any other picture. This publication describes a salt screening – albeit at a later stage of the development process and in a more structured way than the more pragmatic approach commonly used – also with (just) 7 different salts, including the salts mentioned above. The description does not include any indication that in the case at issue, in contrast to common practice, an exhaustive salt screening was nevertheless performed, based on which the patent proprietor was able to make a deliberate choice for these specific salts alone. For this reason, the average skilled person will not assume that paragraph 7 is based on such an exhaustive salt screening or that, with this paragraph, the patent proprietor only envisaged conferring protection for these salts for use with rosuvastatin, notwithstanding the wording of claim 1 in which no restriction regarding the type of salt is included (other than the usual restriction that the salt must be non-toxic and pharmaceutically acceptable).

5.21 Nor does the description or the prosecution file offer any indication for the existence of an underlying (legal) problem that may have been a reason for the patent proprietor to waive part of the protection offered by claim 1 of the patent. Nor did Resolution advance a sufficiently substantiated argument for this. Resolution merely speculated that by not also claiming (according to Resolution) salts other than those mentioned in paragraph 7, the patent proprietor wanted to avoid possible sufficiency of disclosure problems across the whole gamut of the claims. However, Resolution failed to substantiate in any way why the average skilled person would assume this, nor did Resolution conduct any ‘Gillette defence’ in the sense that if the patent would not be interpreted strictly in the sense advocated by Resolution, the patent would be invalid on account of insufficiency of disclosure.

5.22 All of the above leads to the conclusion that on the priority date, the average skilled person did not have valid reasons to assume that the patent proprietor wanted to limit his patent to the salts for use with rosuvastatin mentioned in paragraph 7 and in so doing wanted to waive part of the protection to which he was entitled by virtue of the literal wording of claim 1. Or, in other words, the average skilled person would not assume that the patent proprietor deliberately opted to exclusively confer protection for the salts of rosuvastatin mentioned in paragraph 7. Therefore, he would not consider the list provided in paragraph 7 to be exhaustive. This means that claim 1 must be interpreted such that the extent of the protection it confers extends to (in addition to the rosuvastatin acid) all non-toxic pharmaceutically acceptable salts of rosuvastatin, including those that are not mentioned in paragraph 7 of the description. Moreover, even independent of the ‘valid reasons for the waiver doctrine’, based on the findings in par. 5.14-5.24, the same conclusion would be arrived at.

5.23 Reasonable legal certainty does not object to this interpretation of the claim. Because the average skilled person would not understand paragraph 7 to be exhaustive, in a restrictive sense, and thus, in contrast to what Resolution contends, does not rely on this paragraph to interpret the claim, he

is not misled if the claim is interpreted in accordance with the clear, literal wording of the claim. On the contrary, the reasonable protection for the patent proprietor would be at issue if despite the (much) broader inventive idea, the claim would be interpreted in the more limited sense advocated by Resolution.

5.24 Nor does this interpretation constitute any 'interpreting away' a feature from the claim, as Resolution alleges. After all, the interpretation pertains to the claim feature '*or a non-toxic pharmaceutically acceptable salt thereof*'. As follows from the findings in par. 5.11 above, the starting point is not that paragraph 7 must first be read into the claim to subsequently interpret the claim that has been limited in this way, something that Resolution apparently and wrongfully starts from.

5.25 Nor is this interpretation based on the abandoned essence doctrine, which already follows from the fact that the extent of the protection conferred by the claim as interpreted is more limited than the extent of the protection if only the broader inventive idea had been started from. The inventive idea is just one of the points of view taken into account in interpreting the claim feature in light of the description viewed as a whole, from the perspective of the average skilled person, taking into account his general professional knowledge on the priority date.

Added subject matter

5.26 Resolution takes the position that claim 1 of EP 471 is invalid due to breach of Section 75 (1) c ROW (added subject matter) to the extent that the claim pertains to anything other than rosuvastatin sodium or calcium salt, because the original application allegedly does not directly and unambiguously disclose rosuvastatin acid or other salt forms to the average skilled person. The District Court held that only rosuvastatin acid constitutes added subject matter.

5.27 The original application discloses a new group of statins and claims this group by means of a Markush formula, in which the R1-R4 and X groups can be varied. By way of example of this group of statins, rosuvastatin is disclosed, in example 1 as sodium salt and in example 7 as calcium salt (and further also as alkyl ether). In these examples, the same choices have been made for the R1-R3 and X groups; for the R4 position, sodium, calcium and methyl have been selected from the possibilities mentioned. The original application states that '*hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt*' could be selected for the R4 position.

5.28 As found before, on the priority date, it was part of the average skilled person's general professional knowledge that the biological activity of a statin lies in the anion and that the statin acid or salt form exclusively serves to administer the active ingredient in tablet form. After intake, the acid or salt will dissolve in the body, releasing the active anion. In accordance with this, the potency of different statins (including rosuvastatin) is studied in the 'Experiment' in the original application and not different acid or salt forms of one statin. After all, the acid or salt form chosen is irrelevant for the efficacy (in the sense of biological activity, namely the HMG-CoA reductase inhibitory effect).

5.29 The foregoing means that with the rosuvastatin disclosed in the application, the average skilled person would also read – or, in other words, be reminded of – the possible choices for R4 other than sodium or calcium, i.e. the acid form and other salt forms, as well. Because this choice is not relevant for the biological activity of rosuvastatin, this does not provide any (technical) information that cannot be directly and unambiguously inferred from the original application. Nor is any inadmissible generalization involved. Rosuvastatin is a newly discovered statin, with specific fixed choices on R1-R3 and X; the biological activity is independent of the acid or salt form chosen. Position R4 determines the acid or salt form. Hydrogen (meaning the hydrogen ion that the acid form produces) and cations that can form non-toxic pharmaceutically acceptable salts with a statin are already explicitly mentioned in the original application as belonging to the group from which the parameter for the R4 position can be selected. The explicitly disclosed sodium and calcium salts from this group are examples of this – which the skilled person takes to be non-exhaustive (on p. 4, lines 29-30 of the original application, these examples are also referred to as '*not to be considered as limiting*'). Sodium and calcium belong to the most frequently used salts for pharmaceutical preparations in salt form, but the application does not offer the average skilled person any reason to assume that there is any specific reason to opt for these salts. For this reason, the average skilled person understands that he can vary the R4 position with one of the other ions mentioned, without this having any impact on the biological activity of the explicitly disclosed rosuvastatin. It follows from the preceding findings regarding the interpretation of claim 1 that in contrast to the District Court, the Court of Appeal believes that the average skilled person is reminded of the hydrogen ion and all cations that produce a non-toxic pharmaceutically acceptable salt and not only those mentioned on page 2, lines 42-45 of the application (which corresponds to paragraph 7 of the patent specification).

5.30 It is not clear why all this would be different, because in addition to rosuvastatin, other statins are also disclosed (thus with other choices for R1-R-3 and X), as Resolution alleges (paragraph 36 of the written pleadings in the first instance). After all, the application demonstrates to the average skilled person what the invention is about, namely that a new group of statins has been found, of which in any event the statins mentioned in the Experiment are more potent than any known statin from the prior art. On the same basis as explained before regarding rosuvastatin, each of the statins explicitly disclosed in the examples are directly and unambiguously disclosed in every acid or salt form from the R4 group. The issue is the biological activity of the statin, not the acid or salt form in which the statin can be administered as a tablet, as the average skilled person knew on the priority date.

5.31 The fact that the average skilled person was unable to predict in advance whether and to what extent in practice the acid form and salt forms of rosuvastatin would actually be suitable for use in a pharmaceutical preparation with rosuvastatin, as Resolution contends, does not stand in the way of the direct and unambiguous disclosure in the application of the acid form and salt forms claimed in claim 1 of EP 471. Non-effective salt forms do not fall under claim 1, because this claim only claims pharmaceutically acceptable salts. It is pointed out that Resolution – on whom the duty to contend facts and circumstances and, if necessary, the burden of proof falls in this regard – has not advanced a sufficiently substantiated argument based on which it must be assumed that the average skilled person would nevertheless not also read hydrogen (with which the acid is formed) or any cation with which a salt of rosuvastatin can be formed as a real possibility on the R4 position, despite the fact that

this is explicitly mentioned in the application. With regard to the acid form, Resolution referred to the publication by Berghe from 1977 (*Pharmaceutical Salts, Journal of Pharmaceutical Sciences*, Vol. 66, 1), which notes – not specifically regarding statins – that '*most organic acids and bases are only poorly soluble in H2O*'. However, this is insufficient, in part in light of Astrazeneca's argument, with reference to statements by the experts testifying on its behalf: Spargo (3rd statement, par. 3-8 and the publication of T.M. Serajuddin regarding different statins mentioned here (*Journal of Pharmaceutical Sciences*, Vol. 80, 9), which discloses that polar statins such as rosuvastatin have fair solubility as a free acid) and Frijlink (1st statement, par. 6-11) that the average skilled person will consider the free acid and a salt to be virtually identical. Nor has Resolution challenged that claim 1 is sufficiently disclosed.

5.32 Based on the above, the Court of Appeal believes that no added subject matter is involved, because claim 1 of EP 471 also extends to rosuvastatin acid as well as non-toxic pharmaceutically acceptable salts other than the sodium and calcium salt.

In the cross appeal

5.33 Resolution directed a ground for appeal against the District Court's finding that the salt forms of rosuvastatin other than the sodium and calcium salt are also directly and unambiguously disclosed in the original application. As follows from the findings in par. 5.26-5.32 above, this ground for appeal is unsuccessful.

5.34 Resolutions second ground for appeal is directed against the District Court's finding that Resolution does not have any interest in the revocation of the patent in addition to nullification of the SPC. This ground for appeal cannot help Resolution, because the District Court's judgment will be set aside and the Court of Appeal finds that the SPC is valid.

in the appeal on the main issue and in the cross appeal

Conclusion

5.35 The conclusion is that the Court of Appeal finds that no added subject matter is involved and that rosuvastatin zinc is covered by the extent of the protection that is conferred by claim 1 of EP 471. For this reason, the District Court's judgment must be set aside; Resolution's claims will be dismissed as yet, taking into account that in view of the findings in par. 5.22 and 5.32, the rosuvastatin zinc of Resolution falls under EP 471 and therefore this patent is directly infringed. With this state of affairs, Resolution does not have any interest in its declaratory judgment to the effect that it does not infringe indirectly.

Costs of the proceedings

5.36 As the party ruled against, Resolution will be ordered to pay the costs of the proceedings in both instances. The parties have agreed that the costs of the proceedings in the first instance can be estimated at EUR 240,000.00 and on appeal at EUR 200,000.00.

6. Decision

In the appeal on the main issue and in the cross appeal:

- sets aside the challenged judgment and, in a new judgment:
- dismisses Resolution's claims;
- orders Resolution to pay the costs of the proceedings, on the part of Astrazeneca in both instances estimated at EUR 440,000.00;
- declares the order to pay the costs of the proceedings provisionally enforceable.

This ruling was rendered by R. Kalden, LL.M., M.Y. Bonneur, LL.M. and C.J.J.C. van Nispen, LL.M. and was declared at the public hearing of 16 February 2016 in the presence of the registrar.