

Internal distribution code:

- (A) [-] Publication in OJ
- (B) [-] To Chairmen and Members
- (C) [-] To Chairmen
- (D) [X] No distribution

**Datasheet for the decision
of 10 December 2015**

Case Number: T 2151/12 - 3.3.07

Application Number: 06762303.3

Publication Number: 1901736

IPC: A61K9/20, A61K9/28, A61K31/366,
A61K31/397

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION COMPRISING SIMVASTATIN AND EZETIMIBE

Patent Proprietor:
KRKA, tovarna zdravil, d.d., Novo mesto

Opponent:
Merck Sharp & Dohme Corp.

Headword:
PHARMACEUTICAL COMPOSITION COMPRISING SIMVASTATIN AND
EZETIMIBE/KRKA, tovarna zdravil, d.d. Novo mesto

Relevant legal provisions:
EPC Art. 100(b), 54, 56

Keyword:

Sufficiency of disclosure - (yes)

Novelty - (yes)

Inventive step - (yes)

Decisions cited:

Catchword:



Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent
Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89
2399-4465

Case Number: T 2151/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 December 2015

Appellant: Merck Sharp & Dohme Corp.
(Opponent) 126 East Lincoln Avenue
Rahway, NJ 07065-0907 (US)

Representative: Hussain, Deeba
Merck & Co., Inc.
Patent Department
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU (GB)

Respondent: KRKA, tovarna zdravil, d.d., Novo mesto
(Patent Proprietor) Smarjeska cesta 6
8501 Novo mesto (SI)

Representative: UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
22607 Hamburg (DE)

Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 25 July 2012
rejecting the opposition filed against European
patent No. 1901736 pursuant to Article 101(2)
EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
D. T. Keeling

Summary of Facts and Submissions

- I. European patent No. 1 901 736 based on application No. 06 762 303.3 was granted on the basis of a set of 12 claims.

Independent claim 1 as granted read as follows:

"1. A pharmaceutical composition comprising simvastatin and ezetimibe, wherein no antioxidants are included."

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

- III. The present appeal lies from the decision of the Opposition Division to reject the opposition (Article 101(2) EPC). The decision was based on the claims as granted.

- IV. The documents cited during the opposition proceedings included the following:

(1): WO9508532

(2): US5846966

(3): WO2004/10993

(4): Product leaflet for Simvastatin/ezetimibe - INEBY

(6): Tetrahedron, Vol. 49, no 21, pp 4447-4462 (1993)

(7): Journal of Pharm. Sc., Vol. 90, 253-269 (2001)

(10): Simvastatin: Analytical profiles of drug substances and excipients, Vol. 22, 359-388 (1993)

(11): ICH Harmonized Tripartite Guidelines

(17): Test Report by KRKA

(19): Test report by KRKA

(23): Test report by KRKA

(24): ICH Harmonized Tripartite Guidelines: Stability testing of new drug substances and products Q1A (R2)

V. According to the decision under appeal, document (1) was not novelty destroying, since multiple selections had to be made among the lists of active agents and excipients to arrive to the claimed subject-matter. Document (2) did not disclose the presence of ezetimibe, and the statins were disclosed in a list. Therefore, it was not relevant for novelty.

As regards inventive step, document (3) was considered to be the closest prior art, since it provided compositions comprising ezetimibe and simvastatin. The subject-matter of the claims as granted differed from the disclosure of document (3) in that an antioxidant was not specifically included. The technical effect was a chemically stable composition, and the objective problem the provision of an alternative chemically stable ezetimibe and simvastatin composition.

The assay provided by the opponent could not be used, since the compositions tested did not include an example of the patent and thus a direct comparison could not be made, and since the production methods and conditions of storage were not provided. The missing information was filed by the opponent, but this filing was considered to be late and was not admitted into the opposition proceedings.

The comparative test provided by the proprietor in documents (17) and (19) showed less impurities compared to the closest prior art and therefore inducted a better stability. The opposition concluded that the claimed subject-matter involved an inventive step.

As regards disclosure, the patent as granted provided adequate information on how to provide a composition

comprising ezetimibe and simvastatin without an antioxidant. The absence of packaging details in claim 1 was not considered essential to carry out the invention. The claimed subject-matter was thus considered to be sufficiently disclosed.

- VI. The opponent filed an appeal against said decision. With the statement setting out the grounds of appeal the appellant submitted the following item of evidence:
(25): Test report by Merck
- VII. With a letter dated 20 June 2013, the respondent filed auxiliary requests 1 to 4 and submitted the following items of evidence:
(26): Sama et al., J. Pharm. Sci. & Res. Vol.2(2), 2010, 82-89
(27): Declaration of Mr Andrej Gartner, dated 20.6.2013
(28): ICH Guidelines Q 1 E, Evaluation of Stability Data, August 2003
(29): Declaration of Mr Rade Raskovic
- VIII. With a letter dated 28 June 2013, the respondent filed new auxiliary requests 1 to 4 and submitted the items of evidence (27) and (29) in signed form.
- IX. A Board's communication dated 18 September 2015 was sent to the parties.
- X. With a letter dated 10 November 2015 the appellant submitted a new the item of evidence:
(30): test report update of document (25)
- XI. Oral proceedings took place on 10 December 2015
- XII. The arguments of the appellant may be summarized as follows:

Claim 1 as granted lacked novelty over documents (1) and (2). Both documents disclosed compositions of simvastatin and ezetimibe in a carrier. Antioxidants, fillers, binders and disintegrants were given as examples of excipients of said carrier and both documents disclosed compositions with any or more of the listed carriers, and consequently specifically disclosed compositions of simvastatin and ezetimibe containing excipients other than antioxidants.

As regards inventive step, claim 1 was considered obvious over any of documents (1), (2) and (3). Document (3) disclosed compositions of ezetimibe and simvastatin which included antioxidants such as BHA. The difference between claim 1 and the compositions of document (3) was the exclusion of antioxidants. The effect of this omission would be the prevention of degradation products caused by the presence of antioxidants in the composition. However, the effect would also have been that a greater amount of simvastatin would be oxidized and consequently there would be more degradation products caused by oxidation of simvastatin in the compositions. Thus the compositions of claim 1 contained fewer degradation products from antioxidants but greater degradation products from oxidation of simvastatin. Thus, starting from document (3), the problem addressed by claim 1 could be considered to be the production of compositions which contained fewer degradation products caused by antioxidants. The obvious solution was to omit antioxidants from these formulations. The problem considered by the opposition division, namely the provision of alternative chemically stable ezetimibe and simvastatin compositions was not solved by the opposed patent, since the compositions of the patent

would contain more degradation products than the prior art compositions. This was confirmed by the data submitted by the appellant, in example 1 of the contested patent, and in documents (17), (19) and (23). In summary, the experiments carried out by the patentee found more degradation products to be detected with UV at 230 nm in the compositions containing antioxidants relative to compositions without antioxidants and did not detect any auto oxidative degradation products with UV at 210 nm, 242 nm and 290 nm in compositions with and without antioxidants. It is particularly pointed out that the method of analysis used by the patentee could not have detected all the degradation products present in the tested compositions. It was therefore not possible to conclude from the experimental data provided by the patentee whether the compositions of the patent were more stable or contained less degradation products than the prior art compositions.

A stability analysis had to include a measurement of simvastatin present in the compositions to be conclusive. This measurement was not included in the experimental data provided by the patentee, which measured the amounts of degradation products detectable with UV at 210 nm, 230 nm, 242 nm and 290 nm. The additional experiments (25) provided by the appellant, especially the assays performed at 205 nm, showed the compositions of the patent were found to be less stable and contained more degradation products than the composition in document (3). In particular, there was a greater amount of simvastatin and a lower amount of degradation products after 4 weeks and 8 weeks in the compositions comprising an antioxidant.

As regards the experiments provided by the respondent, these tests only measured the amount of hydrolytic

degradation products, in view of the wavelengths chosen, and not the oxidation degradation products.

The wavelengths of 210, 242 and 290 nm used in document (29) were useless to detect such products.

As regards sufficiency of disclosure, the patent defined the problem as the development of compositions which were more stable and contained less degradation products than the compositions of the prior art. The patent had not solved the proposed problem and the skilled person would not be able to carry out the alleged invention.

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

The claimed subject-matter was novel, because in each case of document (1) or (2) a selection from at least two lists had to be made in order to arrive at the claimed composition.

Document (3) was considered to be the closest prior art and the claimed subject-matter differed in the exclusion of antioxidants. Antioxidants such as BHA and BHT were harmful in higher concentration; the invention aimed thus to avoid the disadvantages associated with such compounds. The technical problem as defined in the description of the patent and formulated by the opposition division was the provision of alternative chemically stable ezetimibe and simvastatin compositions and the solution to thus problem was solved by compositions without antioxidants.

The proprietor conducted several tests showing that compositions of the invention were at least as stable as compositions according to the closest prior art. These test were performed according to the ICH Guidelines, at 15°C and 60% relative humidity (H), while accelerated

studies were performed at 40°C/75%RH (see document (24)).

Document (17) showed that in the tablets of the present invention less degradation products were formed than in all other tablets tested and even more surprisingly in reduced oxygen partial pressure atmosphere.

The test report (19) showed that no oxidation products were seen in the tested tablets according to the invention.

Documents (23) and (27) showed that the compositions of the invention met the ICH stability requirements for a drug product.

In document (29), the proprietor determined the stability of the compositions described in appellant's test (25), but could not repeat them because the mobile phase was not defined. The patentee used the method given in document (26) for determining the amounts of simvastatin and ezetimibe and found that the tablets tested by the appellant in document (25) were stable if subjected to accelerated stability testing according to ICH Guidelines. The test provided in document (29) were performed under air atmosphere and showed no significant loss of simvastatin in composition according to the invention and less degradation products therein.

The tests provided by the patentee were appropriate for analyzing the claimed products, since established tests were used for said analyzes. Document (6) showed that autooxidation of simvastatin primarily resulted in oligomers, and suggested the use of detection wavelengths of 210, 242 and 290 nm. The UV absorption of simvastatin is characterized by absorption maxima at 231, 238 and 290 nm. In document (17) the patentee used the same wavelengths than in the patent, namely 230 nm, very close to the figures of document (6) and in document (19) the method of document (6) was used. In document (23) and (27) the detection was made at 236 nm.

As to the assay of the degradation products, the wavelength of 210 nm used in document (29) was very close from 205 nm used by the appellant in document (25), and was appropriate to detect the same products, given the proximity.

Finally, the stability of of the claimed product is also confirmed by the fact that the product obtained a marketing authorization in Slovenia, as shown by document (31).

As to the tests provided by the appellant, the solvent system was not given in method 2 of document (25) which and made this method unrepeatable and rendered impossible the evaluation of the experiments, since the solvent system was an essential parameter for HPLC analysis.

In the appellant's submissions dated 4 December 2012, the appellant submitted additional comparative tests allegedly showing that simvastatin would be more stable in the presence of BHA. The tests were however performed at 50°C/75%RH, which did not correspond to the standard conditions of 25°C/60%RH or 40°C/75%RH of the ICH Guidelines.

The solution to omit stabilizers was not obvious from document (3) or any other document. At the priority date, it was believed that stabilizers were needed to prevent degradation of the active ingredients. The stabilizers blocked different phases of the oxidation process as shown by document (7).

As to sufficiency of disclosure, the appellant had not provided any evidence showing that it was not possible to prepare the claimed compositions.

XIV. Parties and requests

The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed and the patent maintained on the basis of the claims as granted (Main Request) or, in the alternative, that the patent be maintained on the basis of one of the sets of claims filed as Auxiliary Requests 1 to 4 on 20 June 2013.

Reasons for the Decision

1. Main request - Sufficiency of disclosure

The claimed invention relates to a pharmaceutical composition comprising simvastatin and ezetimibe, wherein no antioxidants are included. There is no reason to doubt the achievability of the preparation of such claimed simple composition, all the more so as the description of the contested patent provides additionally numerous examples showing how to obtain it.

As to the doubts expressed by the appellant regarding the resolution of the problem of the development of compositions which were more stable and contained less degradation products than the compositions of the prior art, this point relates to the question of inventive step. These doubts might express a lack of reproducibility of the invention only when such an effect on stability is expressed in the claim, which is not the case. Otherwise, *ie.* if the effect is not expressed in a claim but is part of the problem to be solved, it relates to inventive step.

Consequently, the invention is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

2. Main request - Novelty

Document (1) relates to azetidinone compounds and also to the combination of an azetidinone compound and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis. Ezetimibe is presented as one among numerous possibilities of the azetidinone, as well as simvastatin among numerous possible cholesterol biosynthesis inhibitors, none of them being presented as preferred embodiments (see claims 7, 15, 16 and 17). The specific combination of ezetimibe and simvastatin would thus result from a selection in two long lists of possible azetidinones and HMG CoA reductase inhibitors. Hence, document (1) does not disclose directly and unambiguously the claimed combination of simvastatin and ezetimibe.

The disclosure of document (2) is very close to the disclosure of document (1) and relates also inter alia to a combination of an azetidinone and a cholesterol biosynthesis inhibitor. Ezetimibe is identified in a list of compounds as well as simvastatin (see claims 9, 10). Hence, a multiple selection has to be made and document (2) does not disclose directly and unambiguously the claimed combination of simvastatin and ezetimibe.

Consequently, the subject-matter of claim 1 of the main request is novel (Article 54 EPC).

3. Main request - Inventive step

- 3.1 The present invention relates to dosage forms of medicaments containing as active ingredients simvastatin and ezetimibe, or pharmaceutically acceptable salts thereof. Specifically, for preparations containing simvastatin and ezetimibe, antioxidants are commonly used to stabilize such compositions to prevent degradation and/or other undesired chemical reactions, such as oxidation reactions. The use of such protective compounds may result in the formation of degradation products, which may in turn react with the active substance they were added to preserve in the first place. Degradation products of the latter act as the reactive sites, which trigger degradation reactions of the active substance in a pharmaceutical dosage form. It is therefore highly desirable to provide chemically stable pharmaceutical compositions for the treatment of atherosclerosis and related conditions or for the reduction of plasma cholesterol levels, which do not show the above shortcomings of the known formulations containing simvastatin and ezetimibe (see par. [0001], [0008]-[0010]).
- 3.2 During oral proceedings, both appellant and respondent considered document (3) as the closest prior art. This document discloses stable compositions of simvastatin and ezetimibe in the form of a product with minimal unwanted degradation by-products and desirable shelf-life stability. Said pharmaceutical composition comprises 4 from 1% to 20% by weight of ezetimibe as a cholesterol absorption inhibitor; from 1% to 80% by weight of simvastatin as an HMG-CoA reductase inhibitor such as simvastatin; and from 0.01% to 2% by weight of a stabilizing agent, including antioxidant agents such as, for example, butylated hydroxyanisole (BHA), 2,6-di-tert-butyl-4-methylphenol (BHT), propyl gallate,

ascorbic acid, citric acid, edetate disodium and calcium metabisulphite, with BHA, propyl gallate and combinations thereof being preferred, and a combination of BHA with propyl gallate being most preferred (see page 5). Examples 1 -5 show the presence of a combination of citric acid, propyl gallate and BHA as stabilizing agents, while example 6 shows a composition with BHA alone at a concentration of 0.02% by weight.

As to the possibility of choosing documents (1) or (2) as closest prior art, these documents neither disclose directly and unambiguously a composition comprising simvastatin and ezetimibe, nor address the stability problem of such composition. This disqualifies them as closer prior the art than document (3), both in terms of the problem to be solved and the technical similarities with the claimed composition.

- 3.3 The problem to be solved according to the contested patent is to provide an alternative chemically stable composition comprising simvastatin and ezetimibe.

The problem as formulated by the appellant in its written submissions, namely the provision of a composition which contained fewer degradation products caused by antioxidants could not be acknowledged, since it does not necessarily involve the general stability of the composition, which is evaluated according to all kinds of degradation products and the remaining quantities of active agents.

- 3.4 As a solution to this alleged problem, claim 1 of the main request proposes a composition comprising simvastatin and ezetimibe in particular without any antioxidant.

3.5 It has to be investigated whether there is sufficient evidence supporting the alleged effect. Several experimental data relating to the stability of the compositions comprising simvastatin and ezetimibe were either present in the description of the contested patent or were provided by both the appellant or the respondent.

3.5.1 Experimental data provided by the appellant

The appellant provided document (25) which shows a comparison between the composition of example 6 of document (3), comprising BHA as sole antioxidant, and the same composition excluding BHA. The tablets were packaged in HDPE bottles with a desiccant for the test, and the storage test was performed at 40°C/75% RH after 4 and 8 weeks.

Stability was tested using two analytical methods. Method 1 was optimized for the detection of simvastatin and of the degradation products simvastatin hydroxy acid and dehydrosimvastatin while method 2 was optimized for the detection of oxidative degradation products not detectable by method 1. The methods were performed via HPLC by UV absorbance at 231 nm and a mobile phase of phosphate buffer and acetonitrile 35:65 for method 1 and at 205 nm and an unspecified mobile phase for method 2. The storage test shows a significant greater amount of remaining simvastatin (97.0% versus 94.1% at 4 weeks and 95.4% versus 92.9% at 8 weeks) and a lesser amount of total degradation products in the composition comprising the antioxidant BHA after 4 and 8 weeks (0.66% versus 1.85% at 4 weeks and 1.34% versus 2.50% at 8 weeks).

Document (30) was further provided by the appellant as an update to the data given in document (25), through the extension of the storage test to 13 weeks. The

comparison confirmed that the compositions comprising BHA had a greater amount of remaining simvastatin (95.6% versus 92.0%)and a lesser amount of total degradation products (1.76% versus 3.02%) after 13 weeks.

Additional evidence was given by the appellant in its letter dated 4 December 2102, in the form of a comparison between a formulation without any antioxidant and three formulations comprising BHA at various concentrations. The formulations were tested at 50°C/75% RH. The amount of simvastatin in these four formulations was compared and the experiment showed that the amount of simvastatin after 3 weeks was proportional to the amount of BHA present and thus that simvastatin was more stable in the presence of BHA.

3.5.2 Experimental evidence provided by the respondent

The contested patent provides a comparison between a reference example comprising the active agents in combination with citric acid, propyl gallate and BHA and the composition according to the invention of example 1, thus without any antioxidant. The test was performed in a blister in normal atmosphere (air) in storage conditions of 50°C and 40°C/75% RH for 3 months. The degradation products were detected after 3 months via HPLC by UV absorbance at 230 nm with a mobile phase of ammonium acetate and acetonitrile.

The results disclosed in Tables 1 and 2 show a percentage of impurities after three month which is lower in the composition according to the invention when tested under respectively 50°C and 40°C/75% RH for 3 months, namely respectively of 0.29% and 0.10% of impurities versus 0.62% and 0.42% of impurities.

This test does not indicate any data relating to the amount of total simvastatin present in the composition originally and after 3 months of storage.

Document (29) is a repetition of the test (25) made by the appellant, thus a comparison of the stability of a composition with BHA and a composition without antioxidant. Both compositions were stored at 40°C/75% RH in OPA/ALU/PVC blisters without desiccant for 4 and 8 weeks. Although document (29) further mentions that "the same packaging material was used and submitted in the registration proceedings", it is not possible to conclude from this remark that the compositions were stored under reduced oxygen partial pressure atmosphere, since the mention only refers to the packaging material as such.

A first method of HPLC detection performed at 236 nm with a mobile phase of phosphate buffer and acetonitrile 45:55 showed that there was no significant loss of active agents for both compositions after 4 and 8 weeks. The composition comprising BHA comprised respectively 99.4% and 99.7% of simvastatin after 4 and 8 weeks, while the composition without antioxidant comprised respectively 99.1% and 98.3% after 4 and 8 weeks of storage.

A second HPLC detection method performed at 230 nm with a mobile phase of ammonium carbonate and acetonitrile showed that the composition without BHA saw a lower increase of the degradation product simvastatin acid, namely of 0.08% at 4 weeks and 0.12% at 8 weeks, in comparison to the composition comprising a stabilizing agent, namely of 0.13% at 4 weeks and 0.14% at 8 weeks. The other detections made at 210, 242 and 290 nm showed the absence of degradation products.

Document (27) relates to the evaluation of the stability of a composition without antioxidant. The stability testing was conducted for 6 months at 40°C/75% RH and 12 months at 25°C/60%RH, in a container closure system proposed for marketing, namely in OPA/ALU/PVC blisters in reduced oxygen partial pressure atmosphere. The detection was made at 236 nm and showed residual amounts of simvastatin and ezetimibe within the ICH requirements. According to the document, the stability data were sufficient for a registration application within the EC.

Documents (17) and (23) are identical and compare a composition without stabilizing agent with several compositions comprising various stabilizing agent(s) under normal atmosphere or under reduced oxygen partial pressure and stored at 40°C/75% RH for one month. Two figures allow a comparison between said compositions, one referring to the total degradation products without any specification (Figure 1), and the second referring to simvastatin acid (Figure 2). It is shown that the amount of degradation products in the composition without stabilising agents (example 2) is less than in other compositions comprising one or more stabilising agents. These documents are silent as to the detection method used, and as to the quantities of simvastatin remaining after one month of storage.

Document (19) compares a composition comprising citric acid, propyl gallate and BHA to the same composition without antioxidants at storage conditions of 40°C/75% RH during one month in aclar blisters. The chromatographic detection was performed at UV wave lengths of 210, 242 and 290 nm. From the chromatogram it was detected that no degradation products were present in either sample exposed under given storage conditions.

This document confirms the results obtained at these wavelengths in document (29).

Document (24) from the European Medicines Agency gives the ICH criteria for stability testing. It discloses that the storage conditions to be used to realise stability tests are 25°C/60% RH during 12 months, 30°C/65% RH for 6 months, and 40°C/75% RH for 6 months. It mentions that if a "significant change" occurs during the 6 months testing, such as a "5% change in assay from its initial value, additional testing should be made" (see pages 12 and 13).

Document (31) is the Slovenian marketing authorization for a medicament comprising ezetimibe and simvastatin without stabilizing agent and according to the claimed composition delivered in December 2013.

3.5.3 Conclusions

It is immediately obvious that the experimental evidences presented by the appellant and by the respondent are systematically contradictory as regard either the amount of remaining simvastatin after storage or the amount of degradation products after storage.

The Board is not in a position to contest technically the results of any experiment provided by both the appellant or the respondent, and has to presume that all data presented reflect the reality. However, it appears that some of said experimental data presented by both the appellant and the respondent present obvious weaknesses, are useless or are not exploitable, namely:

- (a) Both documents (25) and (30) provided by the appellant fail to indicate which solvent system was used in the HPLC method 2 for assaying the

oxidative degradation products not detectable by method 1. The omission of this essential chromatography parameter not only prevents rendering the results of test method 2 verifiable, but also prevents it from being exploitable since it is not possible to determine which degradation products have been assayed in method 2.

- (b) The experiments presented by the appellant within the letter dated 4 December 2012 have been performed under more drastic storage conditions than the usual standard storage test conditions, such as those from the ICH storage test conditions (see document (26)). As mentioned by the respondent, at higher temperatures, thermal instability might become a problem, and thus such a result could have been expected. The experiment therefore cannot be taken into consideration.
- (c) The method of measurement of the amount of degradation products is not given in documents (17) and (23) provided by the respondent, and thus their results are neither verifiable nor exploitable and are impossible to evaluate.
- (d) The experiments of document (27) provided by the respondent relate to a product which is stabilized through reduced oxygen pressure atmosphere. The conduct of the tests at reduced pressure in this document disqualifies it as a relevant document for assessing the existence of an effect, since a reduced pressure is a condition which does not correspond to the subject-matter claimed in claim 1 of the main request.
- (e) The experiments of document (19) provided by the respondent are redundant with the experiments performed in document (29). They confirm the experimental results provided by document (29) as

regards the degradation products detectable at 210, 242 and 290 nm and as such are useless.

Thus, there only remains the measurements made in method 1 of document (25) or its update (30) by the appellant, and the measurements of the contested patent and of document (29) on the simvastatin assay by the respondent. In particular the assays which measure the amount of simvastatin are considered to be essential tests for assessing drug stability, for obvious reasons. Document (25) or its update, document (31), and document (29) provide on this point contrary and contradictory evidence. The Board thus finds itself confronted with two close sets of tests of the parties leading to contradictory results.

The Board notes first that the *modus operandi* used in documents (25) and (30) includes the package into containers including a desiccant which, as mentioned by the respondent, might reduce the hydrolytic degradation of simvastatin into simvastatin acid acid and thereby reduce the negative impact of the presence of antioxidant on simvastation.

The Board notes also that the simvastatin assay as performed in document (29), namely by HPLC with a solvent system of phosphate acetonitrile 45:55 and detection by UV at 236 nm shows that the loss of simvastatin is not significant after 4 and 8 weeks. In other words, when the *modus operandi* of the HPLC chromatography of document (29) is used, the skilled person would not state a significant loss of simvastatin after storage during 4 or 8 weeks.

Finally, the claimed composition received a marketing authorization, as stated by the respondent and shown by document (31), and as such necessarily met the required

criteria of stability, i.e. that the stability of the composition is acceptable according to the ICH Guidelines. No evidence of the contrary is to be found in the file, and this point has not been contested by the appellant.

Under these circumstances, it appears plausible that a composition comprising simvastatin and ezetimibe without antioxidant is chemically stable, so that the problem of providing an alternative composition vis-à-vis of the closest prior art is credibly solved.

3.5.4 Further arguments from the appellant

The appellant argued that the method of analysis used by the respondent, especially as regards the choice of the UV wavelengths used for the detection of the degradation products was unlikely to detect all degradation products present in the formulation.

The Board was not persuaded by this argument. Document (25) used the wavelengths of 231 nm, 238 n and 205 nm to assay respectively dehydrosimvastatin and simvastatic acid, simvastatin and oxidative degradation products. These wavelengths were practically identical to the 230 nm, 236 nm and 210, 242, 290 nm used in document (29), and the slight difference cannot affect the results of the analyses and it is technically not credible that this wavelengths would not have detected the same products.

3.6 It remains to be decided whether, in view of the available prior art documents, it would have been obvious for the skilled person to prepare compositions comprising ezetimibe and simvastatin without an antioxisant.

The sensitivity of simvastatin to oxidative degradation is widely known, such as shown by documents (6) or (10) (see document (6) page 4454; see document (10), page 382).

To solve this problem, document (3) advocates the use of an antioxidant, and more preferably a combination of antioxidants (see page 5, lines 1-10; claim 1; examples). It thus teaches away from the solution of avoiding an antioxidant.

The necessity of using an antioxidant to stabilize simvastatin is also emphasized by document (7) (see page 264, right column). So does the teaching of documents (4) or (5) which relate to marketed product comprising simvastatin, which comprises respectively a combination of BHA and citric acid or of BHA, ascorbic acid and citric acid as stabilizing agents (see document (4), page 21; document (5) page 15).

The other cited documents do not relate to compositions comprising simvastatin.

None of the cited prior art provides thus an incentive to remove the antioxidants from a pharmaceutical composition comprising simvastatin, such as in document (3). They teach rather the contrary, namely the necessity to use an antioxidant or even more a combination of antioxidants to stabilize simvastatin from oxidative degradation.

The solution according to the subject-matter of claim 1 is therefore not obvious.

3.7 The main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



K. Boelicke

J. Riolo

Decision electronically authenticated