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**Datasheet for the decision
of 1 December 2016**

Case Number: T 0292/13 - 3.3.07

Application Number: 03731404.4

Publication Number: 1530459

IPC: A61K9/48, A61K31/4745

Language of the proceedings: EN

Title of invention:

ORAL PHARMACEUTICAL COMPOSITION FOR SOFT CAPSULES CONTAINING
VINORELBINE AND METHOD OF TREATMENT

Patent Proprietor:

R.P. Scherer Technologies, LLC

Opponent:

Moyano Antonia

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - main request (no)
Inventive step - auxiliary requests (no)



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Case Number: T 0292/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 1 December 2016

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Decision under appeal: **Interlocutory decision of the Opposition**
Division of the European Patent Office posted on
28 November 2012 concerning maintenance of
European patent No. 1530459 in amended form.

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
I. Beckedorf

Summary of Facts and Submissions

- I. European patent No. 1 530 459 based on European patent application No. 03731404.4 was opposed on the grounds that its subject-matter lacked novelty and inventive step and was not sufficiently disclosed.

The following documents were among those cited during the first-instance proceedings:

O1: Gazzetta Ufficiale della Repubblica Italiana,
No. 188, 2001, 50-51

O2: Annals of Oncology, 12, 2001, 1683-1691

O4: Annals of Oncology, 12, 2001, 1643-1649

- II. By an interlocutory decision posted on 28 November 2012, the opposition division maintained the patent in amended form on the basis of the patent proprietor's second auxiliary request, filed during the oral proceedings held on 24 October 2012.

Claim 1 of this request read as follows:

"1. An oral pharmaceutical composition including a soft capsule and a liquid fill composition suitable for a soft capsule dosage form encapsulated in the soft capsule, said fill composition including:

a) vinorelbine tartrate in an amount ranging from 5 mg to 100 mg per capsule, wherein the fill composition includes 15.8% of the vinorelbine tartrate;

b) 2.9% of ethanol;

c) 7.1% of water,

d) 1.1 % by weight of glycerol, and

e) 73.1% of polyethylene glycol 400,

all amounts being weight percentages based on a total weight of the fill composition."

III. In the decision under appeal the opposition division came to the conclusion that the subject-matter of the main request and of the first auxiliary request were obvious in view of the teaching of document O1.

As to claim 1 of auxiliary request 2, the opposition division held that the formulation defined in this claim differed from the composition of O1 as regards the amounts of the ingredients. The experimental data disclosed in the patent illustrated the properties of the soft gel capsule of claim 1 in terms of solubility, storage stability, compatibility with capsules material, absence of "dimpling" due to ethanol, maintenance of the bioavailability and viscosity of the fill composition. The prior art did not suggest a combination of the ingredients in the specific proportions defined in claim 1. Thus, the subject-matter of auxiliary request 2 was inventive.

IV. Against the decision of the opposition division an appeal was filed by the patent proprietor (hereinafter: appellant-patent proprietor) and by the opponent (hereinafter: appellant-opponent).

With the statement setting out the grounds of appeal filed on 8 April 2013, the appellant-patent proprietor submitted a main request and three auxiliary requests.

V. The following documents were submitted by the appellants during the appeal proceedings:

O10: Data for regulatory approval of Navelbine soft capsules in Turkey

O11: Data for regulatory approval of Navelbine soft capsules in Russia

O15: Standard shapes and sizes of the softgel dosage form; 1987

- VI. In a communication pursuant to Article 15(1) RPBA issued on 30 September 2016, the Board *inter alia* commented on the requirements of Article 123(2) EPC in respect of the auxiliary requests submitted by the appellant-patent proprietor with the grounds of appeal.
- VII. By letter of 13 October 2016, the appellant-patent proprietor replaced the previous requests by four sets of claims, consisting of a main request and three auxiliary requests.

The main request corresponded to the first auxiliary request forming part of the basis of the decision of the opposition division.

Claim 1 of the main request read as follows:

"1. An oral pharmaceutical composition including a soft capsule and a liquid fill composition suitable for a soft capsule dosage form encapsulated in the soft capsule, said fill composition including:

- a) vinorelbine base in an amount ranging from 5 mg to 100 mg per capsule, wherein the fill composition includes 14% to 18% of vinorelbine tartrate;
- b) 0.3% to 7.5% of ethanol;
- c) 1% to 15% of water,
- d) 0.1% to 20% by weight of glycerol, and
- e) 66% to 78% of polyethylene glycol,

all amounts being weight percentages based on a total weight of the fill composition."

Claim 1 of auxiliary request 1 read as follows:

"1. A liquid oral pharmaceutical composition suitable as a liquid fill composition for a soft capsule dosage form, said composition including:

- a) vinorelbine tartrate present in an amount 14% to 18% of a total weight of the fill composition, wherein the amount of vinorelbine tartrate ranges from 5 mg to 100 mg per capsule;
- b) ethanol present in an amount ranging from 0.3% by weight to 7.5% by weight of the total weight of the fill composition;
- c) water present in an amount ranging from 1% by weight to 15% by weight of the total weight of the fill composition;
- d) glycerol present in an amount ranging from 0.1% by weight to 20% by weight of the total weight of the fill composition;
- e) polyethylene glycol 400 present in an amount ranging from 66% by weight to 78% by weight of the total weight of the fill composition."

Claim 1 of auxiliary request 2 was based on claim 1 of auxiliary request 1 but differed therefrom in that the wording:

"A liquid oral pharmaceutical composition suitable as a liquid fill composition for a soft capsule dosage form, said composition including"

was replaced by:

"An oral pharmaceutical composition including a soft capsule and a liquid fill composition suitable for a soft capsule dosage form encapsulated in the soft capsule, said fill composition including".

Auxiliary request 3 was identical to the request allowed by the opposition division (see point II above).

VIII. Oral proceedings were held on 1 December 2016. Regarding the course of the oral proceedings, reference is made to the minutes.

IX. The appellant-patent proprietor's arguments on inventive step can be summarised as follows:

Document O1 was the publication of the ministerial authorisation for the marketing in Italy of soft capsules containing vinorelbine as the active ingredient. This document was the closest prior art for assessing inventive step. The soft capsules defined in claim 1 of the main request differed from the capsules of O1 in that they contained a higher concentration of active ingredient. This difference implied a reduction of the solvents' percentage. Modifying the composition of the capsules of O1 was not a matter of routine experimentation. Moreover, documents O2 and O4 demonstrated the safety and stability of the liquid fill composition used for the capsules of O1. This would have discouraged the skilled person from modifying the compositions of the capsules of the closest prior art. O1 did not provide any guidance on how to vary the concentrations of vinorelbine and of the solvents while preserving important properties such as stability of the formulation, solubility and the bioavailability of the active ingredient. The reduction of the solvents' percentage in the capsules made it possible to prepare vinorelbine capsules of reduced size which were easier to swallow. Moreover, the experimental data disclosed in the patent and submitted

with the statement setting out the grounds of appeal showed that the capsules of the patent in suit had an improved stability and an increased longevity in storage. In particular, the data disclosed in tables E to G of the statement setting out the grounds of appeal showed a significant advantage of the compositions of the patent in suit relative to the capsules of O1, since the compositions of the patent favoured the degradation of vinorelbine to a metabolite retaining the therapeutic. Table H of the statement setting out the grounds of appeal showed that the capsules of the main request did not show weld defects upon visual inspection after one month or one and half months of storage time. In contrast to this, capsules according to O1 showed weld defects upon storage under the same conditions. The increased longevity in storage was demonstrated by the fact that the capsules of O1 had a shelf-life of 24 months, whereas the capsules of the patent in suit could be stored for at least thirty months, as indicated in O10 and O11. The presence of an inventive step was furthermore supported by the commercial success of the capsules according to the patent in suit. The success was due *inter alia* to the availability of vinorelbine in an oral dosage form to replace injectable formulations, the ease of swallowing of the capsules and their stability.

The same arguments applied to the subject-matter of the auxiliary requests, with the exception of the considerations based on the data disclosed in Table H, which related to compositions not covered by the auxiliary requests.

- X. The appellant-opponent's arguments on inventive step can be summarised as follows:

The composition of claim 1 of the main request differed from the composition of O1 in that it contained a higher amount of active ingredient and a reduced amount of polyethylene glycol. In terms of the absolute amounts of the ingredients, the fill composition of O1 was nearly identical to the compositions of Formula 1 of example 2 of the patent. The data disclosed in the patent were not based on comparative experiments. Hence, they did not demonstrate the presence of improved properties over the compositions of O1. Nor could the experiments submitted with the statement setting out the grounds of appeal be regarded as evidence of an improvement over the compositions of O1. In particular, the data of Tables E to G concerning the ratio of the amounts of metabolites formed upon storage were meaningless without any information as to the absolute amounts of these metabolites. As to the differences in absolute volume of the capsules, these were rather small. Accordingly, these differences had no significant impact on ease of administration. Comparing the shelf lives of the products disclosed in O10 and O11 with the shelf life of the products of O1, as suggested by the appellant-patent proprietor, was meaningless, since the experiments for the products of O10 and O11 had been carried out many years after the experiments for the products of O1. Furthermore, the marketing authorisations O10 and O11 related to the same capsules disclosed in O1. For all these reasons there were no unexpected or surprising technical effects due to the increase of vinorelbine concentration in the capsules. The compositions of claim 1 of the main request were therefore obvious in

that they were nearly identical to the compositions of O1.

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

XI. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of one of the sets of claims filed as main request and as auxiliary requests 1 to 3 with letter of 13 October 2016.

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

Reasons for the Decision

Main request

Inventive step

1. The invention relates to oral pharmaceutical compositions in the form of soft capsules containing the vinca alkaloid vinorelbine as active ingredient (see [0001]).
2. Closest prior art
 - 2.1 It was not disputed by the parties that document O1 represents the closest prior art. O1 relates to the regulatory approval in Italy of a medicament in the form of soft gel capsules containing vinorelbine bitartrate as active ingredient. The document discloses

various dosage forms containing different amounts of active ingredient.

2.2 According to the appellant-opponent's calculation, which has never been contested by the appellant-patent proprietor, the capsules of O1 containing 40 mg of vinorelbine base include:

- 12.5% of vinorelbine tartrate
- 2.3% of ethanol
- 5.6% of purified water
- 0.9% of glycerol
- 78.8% of polyethylene glycol,

all amounts being expressed as weight percentages relative to the total weight of the fill of the capsules.

The composition defined in claim 1 of the main request differs from the composition of O1 described above on account of a higher concentration of active ingredient (14-18% vs. 12.5%) and a slightly lower concentration of polyethylene glycol (66-78% vs. 78.8%).

3. Technical problem

3.1 The appellant-patent proprietor argued that the capsules described in the patent in suit offered various technical advantages over the capsules of O1.

In the following sections the Board will analyse the experimental evidence disclosed in the patent or submitted during the appeal proceedings to determine which technical effects claimed by the appellant-patent proprietor can actually be taken into account for the formulation of the technical problem.

3.1.1 The patent discloses in examples 2 to 6 the results of some tests performed using vinorelbine in soft-capsules or powder form. The tests of examples 2 to 5 relate in particular to the assessment of the "dimpling" phenomenon, the measurement of solubility and the evaluation of stability. Example 6 relates to the assessment of the stability of the material of the capsules, which is not a feature of claim 1. In none of these examples have the soft gel capsules of O1 been tested.

Hence, the experiments of the patent do not allow any comparison to be made between the formulation of claim 1 and the formulation of O1. In the Board's view, since the soft capsules of O1 have received a marketing authorisation, it can fairly be assumed that they will also have an acceptable solubility and stability and that major problems of "dimpling" will not occur.

Accordingly, the experiments disclosed in the patent may be regarded as an indication that the claimed formulation substantially retains certain properties of the formulation of O1.

3.1.2 In section V of its statement setting out the grounds of appeal, the appellant-patent proprietor describes an experiment in which a composition according to O1 was compared with three compositions according to claim 1 of the main request. The experiment consists in storing the compositions under various conditions of temperature and relative humidity and then observing the degradation products formed after one or two months. In particular, the parameter determined is the ratio of the amounts of two degradation products, namely 6'-N-oxyvinorelbine (hereinafter: "6'-N") and

4-O-deacetylvinorelbine (hereinafter: "4-O"). It is explained that the degradation product 4-O is a natural human metabolite which has the same activity as vinorelbine and similar toxicity, while the degradation product 6'-N is a natural human metabolite which has no activity and no toxicity.

The results of the experiment are disclosed in Tables E to G. In the first test carried out at 25°C and 60% relative humidity for two months, the ratio 6'-N/4-O for the composition of O1 containing 12.4% of vinorelbine tartrate is 6.06. For the three compositions according to the patent in suit containing 14.0%, 15.8% and 18% of active ingredient, the ratios 6'-N/4-O are respectively 4.15, 3.38 and 2.52. The results for the tests carried out under different storage conditions invariably show the same trend as the first experiment, namely a higher 6'-N/4-O ratio for the composition of O1 compared to the compositions of claim 1.

Since the degradation product 4-O has the same therapeutic activity of vinorelbine, whereas the 6'-N product is not active (see above), it is correct to conclude that the compositions of the invention provide a more favourable distribution of degradation products upon storage.

However, as pointed out by the appellant-opponent, the experimental report fails to provide any information as to the absolute amounts of degradation products formed, and the mere indication of the 6'-N/4-O ratio does not make it possible to determine these amounts. Such information is however of fundamental importance for evaluating the technical relevance and the concrete consequences of the experimental observations made by

the appellant-patent proprietor. In principle, the total amounts of the degradation products formed upon storage may be very small. In that case the differences between the composition of O1 and the compositions of the invention in terms of amounts of "good" and "bad" metabolites could be so small as to have no practical consequences. This observation applies in particular when the capsules contain very small amounts of active ingredient, close to the lowest point of claim 1, *i.e.* 5 mg. Of course, the Board is not in a position to speculate about this issue. It is however the duty of a party that produces an experiment to provide all the information which is relevant for assessing it. In the present case, in the absence of any data as to the absolute amounts of metabolites formed, the Board is unable to weigh up the technical effect of the experimental observations made by the appellant-patent proprietor and to establish whether they may have any practical consequence.

For this reason the Board does not consider the experiment as evidence of a technical improvement over the closest prior art.

- 3.1.3 Section V of the statement setting out the grounds of appeal of the appellant-patent proprietor contains a further experiment relating to the stability upon storage of the capsules according to claim 1 and of the capsules of O1. One of the parameters considered in this experiment is the presence of defects in the welds of the capsules after a storage period of 1 month or of 1.5 months. All the tested capsules have an oblong shape and contain 80 mg of vinorelbine tartrate. The results reported in Table H indicate that the welds of the capsules of the patent in suit remain normal after

storage, whereas some of the capsules according to O1 show weld defects.

The Board notes that claim 1 of the main request does not contain any limitation as to the material, shape and dimension of the capsules. Document O15, submitted by the appellant-patent proprietor during the appeal stage, shows that several types of capsules characterised by different shapes and sizes were available at the priority date. The experiment carried out by the appellant-patent proprietor is based on visual inspection of the capsules. In the Board's opinion, there is no evidence that the same results reported in Table H would be obtained if capsules of different shape and size were tested.

Thus, this experiment is no proof of a technical effect linked to the distinguishing feature over O1, namely a higher concentration of active ingredient and a slightly lower concentration of polyethylene glycol.

- 3.1.4 The appellant-patent proprietor also argued that the shelf-life periods reported in O10 and O11 for capsules according to the main request were longer than the shelf-life periods reported in O1. This was an indication of improved stability over the capsules of O1.

Document O10 and O11 are the marketing authorisations in Turkey and Russia respectively of capsules containing vinorelbine tartrate. The parties disputed whether these capsules had the same composition as the capsules of O1, as maintained by the appellant-opponent, or whether they corresponded to capsules according to the patent in suit, as maintained by the appellant-patent proprietor.

Independently of this issue, the Board considers that the information reported in O1, O10 and O11 as to the shelf-life of the capsules does not allow any conclusion to be drawn in relation to their stability, as argued by the appellant-patent proprietor. Indeed, there is no indication that the authorities responsible for granting the marketing authorisation in Italy, Turkey and Russia establish the shelf-life of a pharmaceutical product on the basis of the same type of stability data, *i.e.* applying an identical standard. In this respect it is noted that O10 and O11, which according to the patent-proprietor concern the same product, report different storage periods (30 months in O10 and 3 years in O11).

Thus, the information concerning the shelf-lives of the products of O1, O10 and O11 does not support the conclusion that the capsules of claim 1 are more stable than the capsules of O1.

- 3.1.5 The appellant-patent proprietor did not submit any experimental evidence to support its argument that the capsules of the patent in suit were easier to swallow than the capsules of O1.

This advantage is nevertheless credible in the Board's view, since a reduction of the relative amount of polyethylene glycol, which is the main component of the liquid fill composition, will very likely result in a reduction of the capsules' size. It is also evident that this effect will ease the swallowing.

- 3.2 Thus, in the light of the considerations set out in paragraphs 3.1.1 to 3.1.5 above, the objective

technical problem can be formulated as the provision of capsules of vinorelbine which are easier to swallow.

4. Obviousness

- 4.1 Reducing the size of the capsule is in the Board's view a straightforward measure for a skilled person facing the problem defined above, since a small capsule is obviously easier to swallow than a larger one.

Since the major component of the liquid fill composition of the capsules of O1 is polyethylene glycol, the skilled person trying to reduce the size of these capsules will as a first option consider reducing the amount of this excipient. The other excipients (ethanol, water and glycerol) are present in very small amounts (see 2.2 above), so that it would be more difficult to achieve a significant reduction in the capsules' size by reducing them. It is also clear that the skilled person would not consider lowering the vinorelbine load since this would have an impact on the therapeutic efficacy of the capsules.

- 4.2 The capsules of claim 1 differ from the capsules of O1 in having a higher concentration of active ingredient and a lower concentration of polyethylene glycol (see point 2.2 above). For the reasons explained in the previous paragraph, the skilled person confronted with the technical problem defined above would reduce the amount of polyethylene glycol thereby reducing the total amount of excipients. This would imply an increase in the weight percentage of vinorelbine, based on the total weight of the fill composition. The skilled person would thus arrive in an obvious manner at the subject-matter of claim 1.

4.3 The appellant-patent proprietor argued that the person skilled in the art would not have modified the composition of a product which had already received a marketing authorisation. In this respect it remarked that documents O2 and O4 showed that the capsules of O1 were already safe and stable.

4.3.1 The Board cannot follow this reasoning, which would imply that once a pharmaceutical product obtains a marketing authorisation, research in that particular area comes to an end. On the contrary, the Board considers that it is the normal attitude of a researcher to investigate the properties of such a product, to carry out tests on it and to consider modifications that might lead to further improvement.

It is not denied that changing the composition of a pharmaceutical product may be a challenging task. However, in the present case there is no indication in the prior art that reducing the amount of polyethylene glycol in the capsules of O1 would pose insurmountable technical difficulties. Accordingly, the argument that the skilled person would never consider modifying the products of O1 is not convincing.

4.4 The appellant-patent proprietor also invoked the commercial success of the invention as evidence for the presence of an inventive step.

The Board notes that commercial success is referred to in the case law of the boards of appeal as one of the secondary indicia for the assessment of inventive step. Considerations based on the presence of such secondary indicia cannot replace the objective assessment of inventive step applying the problem-solution approach. Secondary indicia are only of importance in case of

doubt, *i.e.* when objective evaluation of the prior-art teachings does not provide a clear picture (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016, I.D.10.1). In the present case the assessment of inventive step based on the problem-solution approach shows that the subject-matter of claim 1 is obvious (see point 4.2 above), with the consequence that there is no doubt that inventive step is lacking.

In addition to the above, the Board notes that the appellant-opponent explains the commercial success of the invention *inter alia* with the argument that it made vinorelbine available in an oral dosage form and with the observation that the capsules are stable. However, since the same considerations apply to the capsules of O1, it cannot be concluded that the commercial success of the product of claim 1 is due to the features that distinguish this product from the product of the closest prior art. Hence, also for this reason, the commercial success of the capsules of claim 1 does not support the presence of an inventive step.

5. For the above reasons, the Board concludes that the main request does not comply with the requirements of Article 56 EPC.

Auxiliary requests 1 and 2

6. These requests were submitted by the appellant-patent proprietor as a reaction to some points made by the Board in relation to the compliance with Article 123(2) EPC of the auxiliary requests filed previously (see VI above).

The main difference between claim 1 of both requests and claim 1 of the main request is that the feature

"vinorelbine base in an amount ranging from 5 mg to 100 mg" has been replaced by "wherein the amount of vinorelbine tartrate ranges from 5 mg to 100 mg per capsule". This amendment does not result in any additional distinguishing feature over the disclosure of O1. The ingredients of the capsules and their relative amounts remain the same as for the main request.

The appellant-patent proprietor did not submit any new argument as to the inventive step of these requests.

The Board considers that the modifications introduced in auxiliary requests 1 and 2 do not affect the conclusion drawn in point 5 above with regard to the main request. Thus, auxiliary requests 1 and 2 do not fulfil the requirements of Article 56 EPC either.

Auxiliary request 3

7. Claim 1 of this request, which corresponds to the request allowed by the opposition division, differs from claim 1 of the main request in specifying, for each component of the composition, the exact weight percentage amount instead of providing a range (see point II above).

7.1 The composition defined in auxiliary request 3 differs from the composition of O1 not only in the amounts of active ingredient and polyethylene glycol but also in the amounts of ethanol (2.9% vs. 2.3%), water (7.1% vs. 5.6%) and glycerol (1.1% vs. 0.9) (see also point 2.2 above).

The evidence on file does not show any technical effect associated with the minor variations in the

concentrations of ethanol, water and glycerol. Nor has the appellant-patent proprietor put forward specific arguments in this respect.

The considerations set out in respect of the main request apply also to the subject-matter of auxiliary request 3. In particular, for the reasons explained in point 4 above, the skilled person seeking to provide vinorelbine capsules which are easier to swallow than the capsules of O1 would consider reducing the amount of the main excipient, namely polyethylene glycol. Such a modification would also entail minor adjustments in the relative amounts of the other components. However, in the absence of any evidence of concrete technical difficulties in carrying out such adjustments, this cannot support the presence of an inventive step.

It follows from the above that the subject-matter of auxiliary request 3 likewise does not comply with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated