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Datasheet for the decision of 8 November 2018

Case Number: T 1938/15 - 3.3.07

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Language of the proceedings: EN

Title of invention:
Pharmaceutical composition containing montelukast

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

Opponent:
ZBM PATENTS, S.L.

Headword:
Montelukast/ KRKA

Relevant legal provisions:
EPC Art. 123(2), 100(b), 56

Keyword:
Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Case Number: T 1938/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 November 2018

Appellant: (Opponent)	ZBM PATENTS, S.L. Pl. Catalunya 1 E-08002 Barcelona (ES)
Representative:	ZBM Patents - Zea, Barlocci & Markvardsen Plaza Catalunya, 1 08002 Barcelona (ES)
Respondent: (Patent Proprietor)	KRKA, tovarna zdravil, d.d., Novo mesto Smarjeska cesta 6 8501 Novo mesto (SI)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 August 2015 concerning maintenance of the European Patent No. 1976522 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	C. Schmidt

Summary of Facts and Submissions

I. European Patent 1 976 522 was opposed on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed. The following documents were among those cited during the first-instance proceedings:

O1: WO 2004/091585;
O2: Singulair® label 1998;
O5: Pharmaceutical dosage forms, Vol. 1, 1989, 195-202
O14: Test report by U. Ocepek, dated 11 May 2015.

II. The opposition division held that the patent and the invention to which it related according to the main request filed on 12 May 2015, met the requirements of the Convention. This decision was appealed by the the opponent (hereinafter "the appellant")

Claim 1 of the main request filed on 12 May 2015 read as follows:

"1. Pharmaceutical composition in the form of a tablet comprising a pharmaceutically acceptable salt of montelukast in amorphous form as the active ingredient, characterized in that it comprises an outer film coating and that the active ingredient is present in the form of particles having a d_{90} value of less than 250 µm and an average particle size within the range of 20 to 150 µm, and that the tablet is prepared by direct compression."

The main request comprised a further independent claim (claim 12) concerning a process for preparing a composition according to claim 1.

III. The opposition division held that the features of claim 1 were directly and unambiguously disclosed in combination with each other in the original application. Hence, the requirements of Article 123(2) EPC were met.

Concerning the sufficiency of disclosure, the opposition division observed that the application as filed did not provide all the details for determining the average particle size of montelukast. It concluded that it was nevertheless plausible to expect that the skilled person would have been able to fill the information gap by referring to his general knowledge.

Document O2, describing the Singulair® tablets was the closest prior art for the assessment of inventive step. O2 did not provide any information as to the process for preparing the tablets. The experiments disclosed in O14 showed that the stability of the montelukast tablets increased when a method of direct compression was used for their preparation. The prior art did not suggest this. The requirement of inventive step was therefore met. The main request was inventive also when starting from document O1 as the closest prior art.

IV. With the statement setting out the grounds of appeal filed on 4 December 2015 the appellant requested that the decision under appeal be set aside and the patent be revoked. It furthermore submitted the following documents:

O21: Experimental report: particle size distribution analysis of montelukast sodium particles;
O22: Malvern Mastersizer "Getting started", 1997, pages 3.5, 4.2, 7.6, 9.1-9.8.

The following additional documents were submitted by the appellant on 4 November 2016:

O27: ISO standard 13320-1 (1999);
O28: Particle characterization report - Nanomol technologies.

V. The patent-proprietor (hereinafter: the respondent) replied to the appeal of the opponent by letter of 20 June 2016 . It requested to dismiss the appeal and filed three auxiliary requests.

VI. On 17 September 2018, the Board issued a communication pursuant to Article 15(1) RPBA in which it expressed the opinion that the main request complied with the requirements of Articles 123(2) and 56 EPC. As to the sufficiency of disclosure, it indicated that the experimental reports submitted by the appellant (O21 and O28) were to be considered during the oral proceedings. The Board further stated that it was of the preliminary opinion that the main request also met the requirement of sufficiency of disclosure.

VII. Oral proceedings were held on the 8 November 2018. They were not attended by the appellant, who had informed the Board accordingly by letter of 3 September 2018.

VIII. The arguments presented in writing by the appellant can be summarised as follows:

(a) Article 123(2) EPC

Claim 1 of the main request combined several features which were disclosed in the original application at different levels of preference. Accordingly, the

subject-matter of this claim could not be directly and unambiguously derived from the original application.

(b) Sufficiency of disclosure

The description of the patent did not provide information on how to carry out the measurement of the particle size of the active ingredient. In particular, no information was given as to the preparation of the sample and as to the conditions for carrying out the laser-diffraction measurements. As explained in document O12, these were crucial aspects of the laser-diffraction analysis. Moreover, the experimental reports O21 and O28 showed that the particle size measurements for a given sample were affected by the conditions under which the analysis were carried out. Thus, the skilled person seeking to reproduce the invention was not in a position to measure with certainty the particle size.

(c) Inventive step

Document O2 was a suitable starting point for the assessment of inventive step. The subject-matter of claim 1 differed from the disclosure of O2 mainly in the indication that the tablets were prepared by direct compression. The experimental data disclosed in the patent did not support an improvement of stability arising from the use of the direct compression technology. As for the experimental report O14, this showed an improvement of stability at most only for a single specific impurity, namely the impurity at retention time (Rt) 2.6 minutes in the HPLC analysis. However, the data of O14 were not consistent with the data of the patent. It was also questionable whether O14 was evidence of an improvement achieved over the

whole scope of claim 1. Accordingly, the technical problem was the provision of an alternative composition of montelukast. The direct compression was a well-known technique for the preparation of tablets. Furthermore, the skilled person would have avoided to use a granulation process since montelukast was a hygroscopic substance. Accordingly, the main request did not comply with the requirements of Article 56 EPC.

The main request was obvious also when starting from O1 as the closest prior art. The tablets of claim 1 differed from those of O1 in the particle size of montelukast and in the presence of an outer coating. However, in the absence of any unexpected effect these distinguishing features did not provide any inventive contribution to the subject-matter of claim 1.

IX. The arguments of the respondent can be summarised as follows:

(a) Article 123(2) EPC

The features introduced in claim 1 were based on preferred embodiments disclosed in the original application. The requirement of Article 123(2) EPC was therefore met.

(b) Sufficiency of disclosure

The description of the patent explained that the particle size was determined by laser light scattering. It furthermore indicated that the measurements could be made with the Malvern-Mastersizer Apparatus. O12 indicated that light scattering was one of the most used techniques for measuring particle size. Information on how to prepare the samples or carrying

out the measurements were disclosed in several documents such as O12, O22 and O27. It was not clear whether the experiments carried out by the appellant were made in accordance with the methods recommended in these documents. It appeared for instance that both in O21 and O28 the samples were not fully dispersed. Thus, the appellant's objection of insufficiency of disclosure was unfounded.

(c) Inventive step

The test report O14 showed that by a method of direct compression it was possible to prepare montelukast tablets containing a reduced amount of the impurity having a retention time of 2.6 minutes. This impurity was the montelukast sulfoxide a product generated by oxidation of montelukast. None of the prior art documents suggested that preparing the tablets by direct compression resulted in a reduction of the sulfoxide impurity. On the basis of this unexpected effect the subject-matter of claim 1 complied with the requirements of Article 56 EPC.

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

XI. The respondent requested to reject the appeal or to maintain the patent on the basis of one of auxiliary requests 1 to 3 filed on 20 June 2016.

Reasons for the Decision

Main request

1. Article 123(2) EPC

1.1 Claim 1 derives from the incorporation in original claim 1 of some features disclosed in the original application. In particular:

(a) the indication that the composition is in form of a tablet comprising an outer film coating and the tablet is prepared by direct compression finds a basis on page 4, lines 15 to 21. Tablets prepared by direct compression are also described as preferred embodiment on page 10, lines 24 to 26. Page 11, lines 8 and 9 states that the tablets are preferably coated;

(b) the indication that montelukast is in amorphous form is disclosed in original claim 10 which refers back to claim 1, and on page 6, line 3;

(c) the average particle size is disclosed in original claim 2 which refers back to claim 1 and in the last sentence of page 4.

1.2 The features included in claim 1 reflect preferred embodiments of the invention. The combination of these features does not result in addition of subject-matter.

Hence, the main request meets the requirements of Article 123(2) EPC.

2. Sufficiency of disclosure

2.1 The appellant's objection in relation to the requirement of sufficiency of disclosure is based on the argument that the description does not provide sufficient information as to the procedures for determining the montelukast particle size. In this regard the appellant observes that the measurement of the particle size may be affected by various factors such as the preparation of the sample and the conditions under which the laser light scattering analysis is carried out. However, the patent would not provide any guidance in this regard.

2.2 Paragraph [0017] is the most relevant part of the description in relation to this issue. It explains that the particle size of the montelukast samples can be determined by laser light scattering using for instance a Malvern Mastersizer apparatus. The size distribution is then determined from the scattering data using the Mie theory.

2.3 The Board agrees with the appellant that various factors may affect the laser light scattering measurement. This conclusion is supported for instance by documents O12, O22 and O27. However, these documents also provide some guidance on how to carry out the measurements and preparing the sample to be analysed. O12, for instance, contains a section dedicated to the preparation of the sample in which information is given in particular in relation to the dispersion procedure (see chapter "Preparation of the sample" starting from page 3). Similar information is disclosed on pages 9.3 to 9.7 of O22. This document also provides a list of the commonly used dispersants and a list of recommended surfactants which may be added to the dispersant. The

procedure for preparing an unknown sample is summarized in a flow diagram depicted on page 9.8 of O22. Documents O27 provides several details as to the measurement procedure, including the setting up of the instrument and the selection of an appropriate optical model (see chapter "Measurement" starting from page 9).

2.4 Thus, although it is evident that some decisions need to be taken when performing the particle size measurements (e.g. selection of dispersant, surfactant etc.), and the patent is silent in this respect, it is also true that the skilled person can follow the general criteria which are known for instance from O12, O22 and O27. In this context it is also noted that laser light scattering is a widely used technique for particle size measurements. According to O12 the popularity of this method "is partly due to the way precise measurements can be made quickly and easily" (chapter 2.9.31, first paragraph).

2.5 The experimental data submitted by the appellant (documents O21 and O28) show that for a given sample of montelukast sodium different particle size distributions can be obtained depending on the method used for preparing the sample and on the measurement procedure.

In the Board's view, these observations are in line with the teaching of O12, O22 and O27 since also these documents indicate that various factors may affect the measurement of the particle size. In the present context, what matters for the assessment of the requirement of sufficiency of disclosure is whether the measurements described in O21 and O28 have been carried out in compliance with the criteria illustrated in O12, O22 and O27.

In its communication of 17 September 2018 the Board indicated that it intended to discuss this issue at the oral proceedings. They were however not attended by the appellant.

2.6 In its written submissions of 20 June 2016 the respondent argued that in O21 the montelukast samples were tested at different levels of dispersion. This was possibly due to the different durations of the ultrasonics treatments. Similar problems were present in the experiments described in O28. In this regard the appellant observed during the oral proceedings that O28 reports a reduction in obscuration values during the measurements (page 11). However, O22 explains that measurements should not be made until the obscuration has stabilized, indicating that the sample was properly dispersed (paragraph 9.7).

2.7 A conclusion of insufficiency of disclosure presupposes that serious doubts exist as to whether the skilled person would be able to carry out the invention having regard to the information disclosed in the patent and using his common general knowledge. Documents O12, O22 and O27 indicate that laser diffraction methods are commonly used and provide accurate results. Although various factors may affect the analysis, it is clear that these factors have extensively been studied and procedures have been developed for guiding the skilled person in performing the measurements. This is particularly evident from O27, a document issued by the International Organization for Standardization (ISO), which is aimed at providing a methodology for adequate quality control in particle size analysis (see "introduction"). The appellant's experiments do not demonstrate in the Board's view that the skilled person

would not be able to determine the montelukast particle size in spite of the abundant information in the prior art with regard to the laser diffraction methods.

In the light of these considerations, the Board concludes that the requirement of sufficiency of disclosure is met.

3. Inventive step

3.1 Closest prior art

3.1.1 The Board agrees with the opposition division that document O2, disclosing the Singulair® tablets, is the closest prior art for the assessment of inventive step.

3.1.2 O1, proposed by the appellant as an alternative closest prior art, relates to orally disintegrating tablets which in contrast to the tablets of claim 1 of the main request are not coated by an outer film. It is clear that in view of the presence of an outer film, the tablets of the opposed patent do not disintegrate orally. Adding an outer film to the tablets of O1 would render them unsuitable as orally disintegrating tablets. In the Board's view, the skilled person would not consider a modification of the tablets of O1 which is contrary to the general purpose of O1 itself. Furthermore, the skilled person confronted with the problem of providing tablets which do not disintegrate in the mouth would not start his research from orally disintegrating tablets and then decide to coat them with an outer film. Such an approach would be based on hindsight.

3.1.3 O2 describes film-coated tablets containing montelukast sodium as active ingredient. This document does not

provide any information as to the method used for preparing the tablets. Thus, at least the feature "prepared by direct compression" distinguishes the tablets of claim 1 over those of O2

3.2 Technical problem

3.2.1 The experimental report O14 provides data on the stability of montelukast tablets prepared by direct compression or wet-granulation.

3.2.2 The results disclosed in the table of page 5 of O14 show an improved stability under accelerated stress conditions for the tablets prepared by direct compression with regard to the impurity at retention time (Rt) 2.6 min in the HPLC analysis. In the letter of reply to the appeal of the opponent, the respondent explains that this impurity is the montelukast sulfoxide which is formed by oxidation of montelukast. The same explanation was given in the letter accompanying the submission of O14, filed during the first instance proceedings on 12 May 2015.

3.2.3 The experimental data disclosed in example 5 of the patent confirm that under certain storage conditions tablets prepared by direct compression are more stable than tablets prepared by wet-granulation with regard to the impurity at Rt 2.6 minutes. However, as noted in the appealed decision, the tablets compared in the patent differ not only in the manufacturing process but also in the composition.

3.2.4 In the statement setting out the grounds of appeal the appellant underlines some inconsistencies between the stability data disclosed in O14 and the data reported in the patent for tablets prepared by the same method.

In this regard the Board agrees with the respondent that experimental data determined in tests carried out in 2015 (O14) cannot be compared with data obtained in different tests carried out 10 years earlier (examples of the patent). There is indeed no evidence that the experiments were carried out under identical conditions, e.g. by using the same instruments and using substances (e.g. excipients and solvents) having the same degree of purity. Thus, the Board considers that there are no inconsistencies in the experimental data submitted by the respondent.

3.2.5 The appellant further argues that there is no evidence that the improvement concerning the reduction of the montelukast sulfoxide impurity could be achieved over the whole scope of the claims. The Board notes in this regard that the respondent has tested tablets prepared by direct compression which contain different types of excipients and montelukast sodium of different particle sizes (see O14 and examples of the patent). In contrast, the appellant did not provide any experimental data or specific technical argument to demonstrate that other factors, in addition to the manufacturing process, may have an impact on the amount of sulfoxide impurity. Hence, this argument of the appellant is unconvincing.

3.2.6 Therefore, the technical problem can be formulated as the provision of montelukast tablets which are stable against oxidation.

3.3 Obviousness

3.3.1 The skilled person was aware before the priority date of the patent-in-suit, that direct compression is a standard method for preparing tablets which is

particularly suitable for the formulation of moisture sensitive active ingredients (see e.g. O5, page 198).

On the other hand, montelukast sulfoxide is a product generated by oxidation of montelukast. Whereas it is known that the direct compression may be useful to reduce the formation of impurities generated by moisture, the prior art is silent on the question whether this technology may be useful also in reducing the impurities formed by processes of oxidation. Furthermore, according to O5 (page 197) the wet granulation technology offers the advantage of reducing air entrapment. Thus, the skilled person facing the problem of reducing the impurities due to processes of oxidation would possibly opt for the wet granulation technology.

3.4 For these reasons, the Board concludes that the subject-matter of claim 1 of the main request meets the requirements of Article 56 EPC. Claim 12 is inventive as well since it relates to a process for preparing the compositions of claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated