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**Datasheet for the decision  
of 9 May 2017**

**Case Number:** T 1256/11 - 3.3.01

**Application Number:** 02777314.2

**Publication Number:** 1438040

**IPC:** A61K31/365, A61K9/28, A61P37/06

**Language of the proceedings:** EN

**Title of invention:**  
PHARMACEUTICAL COMPOSITIONS COMPRISING MYCOPHENOLIC ACID OR  
MYCOPHENOLATE SALT

**Patent Proprietor:**  
Novartis AG  
Novartis Pharma AG

**Opponents:**

**Headword:**  
Tablet preparation/NOVARTIS

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

**Keyword:**

Amendments - added subject-matter (no)

Inventive step - (yes)

**Decisions cited:**

G 0003/14, T 0002/81, T 0925/98, T 1459/05, T 2001/10

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

Boards of Appeal of the  
European Patent Office  
Richard-Reitzner-Allee 8  
85540 Haar  
GERMANY  
Tel. +49 (0)89 2399-0  
Fax +49 (0)89 2399-4465

Case Number: T 1256/11 - 3.3.01

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.01**  
**of 9 May 2017**

**Appellants:**  
(Patent Proprietors)

Novartis AG  
Lichtstrasse 35  
4056 Basel (CH)

Novartis Pharma AG  
Brunner Strasse 59  
1230 Vienna (AT)

**Representative:**

Marshall, Cameron John  
Carpmaels & Ransford LLP  
One Southampton Row  
London WC1B 5HA (GB)

**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
14 January 2011 concerning maintenance of the  
European Patent No. 1438040 in amended form.

**Composition of the Board:**

**Chairman** A. Lindner  
**Members:** G. Seufert  
M. Blasi

## Summary of Facts and Submissions

I. The patent proprietors (appellants) lodged an appeal against the interlocutory decision of the opposition division on the amended form in which the European patent No. 1 438 040 could be maintained.

II. The present decision refers to the following documents:

- (1) WO 97/38689
- (2) GB 1 203 328
- (3) WO 94/12184
- (4) US 5,688,529
- (5) WO 94/26266
- (7) R. Schmouder *et al.* Transplantation, 1999, Vol. 67, No. 7, page S203, abstract 787
- (10) Remington's Pharmaceutical Sciences, 1990, Chapter 89, pages 1633 and 1634
- (12) GB 1 157 100
- (13) R. Voigt, Pharmazeutische Technologie, 9th edition, Deutscher Apotheker Verlag Stuttgart, 2000, Chapter 9, first page
- (14) P. H. List, Arzneiformenlehre, 4th edition, Wissenschaftliche Verlagsgesellschaft 1985, pages 70 to 71
- (22) WO 94/01105

III. Notices of opposition were filed by opponent 1 (Gill Jennings & Every LLP, opponent 2 (Mundipharma GmbH) and opponent 3 (Teva Pharmaceutical Industries Ltd.) requesting revocation of the patent in suit in its entirety on the grounds of lack of novelty and lack of inventive step (Article 100(a) EPC; opponents 1 to 3), insufficiency of disclosure (Article 100(b) EPC;

opponents 1 and 2) and added subject-matter (Article 100(c) EPC; opponent 1).

- IV. With letters of 10 February 2009, 17 November 2009 and 25 October 2010, all opponents withdrew their oppositions.
- V. In a communication of 25 October 2010, the opposition division drew the patent proprietors' attention to Rule 84(2) EPC, according to which the opposition proceedings could be continued by the Office *ex officio*. In a second communication of the same day, the opposition division informed the patent proprietors that the oral proceedings scheduled for 26 October 2010, were maintained.
- VI. The decision under appeal is based on a main request and first to third auxiliary requests, all filed at the oral proceedings before the opposition division.

The opposition division decided that the main request and first to third auxiliary requests complied with Articles 123(2) and (3), 83 and 54 EPC. The subject-matter of the main request and first and second auxiliary requests was held to be obvious starting from any of the documents (1), (7) or (12) as the closest prior art. The subject-matter of the third auxiliary request was considered to be inventive starting from documents (12) or (2) as the closest prior art

- VII. With the statements setting out the grounds of appeal, the appellants filed sets of claims as a main request and first to fifth auxiliary requests (MR, AR1 to AR5).

- VIII. Third party observations were filed by Mr Basfeld, a professional representative, with letter of 26 October 2012.
- IX. With letter dated 4 June 2013, the appellants filed a sixth auxiliary request (AR6), an alternative main request and alternative first to sixth auxiliary requests (MR\* and AR1\* to AR6\*).
- X. Anonymous third party observations were filed on 11 September 2013.
- XI. With letter of 18 January 2016, Mr Basfeld filed further third party observations with the same content as those filed anonymously on 11 September 2013.
- XII. Summons to oral proceedings were sent on 22 December 2016. In a communication dated 31 January 2017, the board drew the appellants' attention to certain procedural issues. It expressed its preliminary opinion and outlined the issues that needed to be discussed.
- XIII. In reply to the board's communication, the appellants provided further arguments in support of their case and filed a main request and first to fifteenth auxiliary requests. The main request and first to sixth auxiliary requests corresponded to the "alternative" claim sets filed with letter of 4 June 2013 (MR\*, AR1\* to AR6\*) and seventh to thirteenth auxiliary requests to the "original" claim sets filed with the statement of grounds of appeal (MR and AR1 to AR5) and with letter dated 4 June 2013 (AR6), with some amendments in auxiliary requests 5, 6, 12 and 13. The appellants also filed two new auxiliary requests.

XIV. At the oral proceedings before the board, the appellant filed a new main request based on the eleventh auxiliary request and withdrew all previous requests.

Claim 1 of the main request, which is the sole independent claim, reads as follows:

"1. A process for the preparation of an enteric coated tablet comprising a pharmacologically effective amount of mycophenolic acid or mycophenolate salt, wherein the mycophenolic acid or mycophenolate salt is present in an amount of from 20% to 80% by weight based on the total weight of the solid dosage form including the enteric coating, wherein the mycophenolic acid or mycophenolate salt is present in substantially anhydrous form which process comprises

- (i) mixing the mycophenolic acid or mycophenolate salt and pharmaceutically acceptable additives,
- (ii) subjecting a mixture obtained in step (i) to granulation,
- (iii) compressing the granulates obtained in step (ii) and pharmaceutically acceptable additives to form the tablet, and
- (iv) applying enteric coating to the mycophenolic acid or mycophenolate salt and/or to the granulates obtained in step (ii) and/or to the tablet obtained in step (iii),

wherein step (ii) and (iv) are carried out applying non-aqueous solvents only, step (ii) being optional.

XV. The appellants' arguments, as far as they relate to the decisive issues of the present decision, can be summarised as follows:



### *Amendments*

The subject-matter of claim 1 of the main request had its basis on page 11, lines 4 to 22 of the application as originally filed. This passage disclosed the claimed process comprising steps (i) to (iv) and specified that the granulation and coating steps were carried out only with non-aqueous solvents. The amount of mycophenolic acid or mycophenolate salt had a basis on page 2, third and fourth paragraphs of the application as originally filed. The range of 20 to 80% was allowable in line with decision T 2/81. The enteric coating was disclosed on page 7, lines 12 to 13 of the application as originally filed.

### *Clarity*

The objection against the clarity of the term "substantially" raised in the third party observations was to be rejected. The expression "in substantially anhydrous form" was used in the claims as granted (see claim 4) and had been incorporated into claim 1 by simple amendment. Under these circumstances, an objection under Article 84 EPC could not be raised.

### *Inventive step*

Document (1) was a suitable starting point for the assessment of inventive step. It concerned enteric coated oral formulations of mycophenolate and disclosed an enteric coated capsule and its preparation. The capsule content contained a relative amount of 16.1% mycophenolate salt.

Document (1) did not disclose the preparation of a tablet. The loading of 20 to 80% was unusually high,

because the physico-chemical characteristic of the active ingredients normally interfered with tablet formation. It would not have been chosen by the skilled person, as it required either high amounts of excipients to obtain tablets with suitable mechanical stability, which would make them undesirably large and inconvenient to administer, or it resulted in tablets with inferior mechanical stability. Sufficient mechanical stability was essential for the enteric coating step. Tablets with low stability were likely to chip, edge, break or crumble.

Document (1) also did not mention the use of anhydrous mycophenolic acid or mycophenolate salts. Nor did it attribute any relevance to that particular form, although it could be deduced from the information given in the examples that an anhydrous form had incidentally been used for the preparation of the capsules. The enteric coating according to document (1) could be carried out with either organic solvents or aqueous solutions.

As already acknowledged in the patent in suit (see paragraph [0055]) the use of the anhydrous form was considered to be advantageous for tablet production. It was found that its conversion into hydrates, which would compromise reproducible tablet production, was avoided by carrying out the coating and granulation step in non-aqueous solvents (see paragraphs [0059] and [0068]). The conversion into hydrates, which could have provided a motive for the skilled person to avoid aqueous solvents in the granulation and coating step, was not disclosed in the art.

The disclosure of documents (3) and (22) was hypothetical and would not have been considered by the

skilled person. Document (12) did not specify the amount of the maize starch paste. The amount of mycophenolic acid was therefore unclear. Document (7), which like document (1) referred to enteric coated tablets, did not specify that the relative amount of the active ingredient was 20 to 80%. It also did not disclose the preparation of such a tablet. None of these documents disclosed the anhydrous form.

XVI. The appellants requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request filed at the oral proceedings before the board.

XVII. At the end of the oral proceedings, the decision of the board was announced.

### **Reasons for the Decision**

1. The appeal is admissible.

2. Amendments (Article 123(2) EPC)

2.1 Claim 1 of the main request is directed to a process for the preparation of an enteric coated tablet with mycophenolic acid or mycophenolate salt in an amount of from 20 to 80% by weight based on the total weight of the tablet via direct compression or granulation and compression, i.e. steps (i) to (iv) (see point XIV above). The mycophenolic acid or mycophenolate salt is present in substantially anhydrous form and the coating and the granulation step are carried out applying only non-aqueous solvents.

2.2 The subject-matter of the claim finds support on page 11, lines 4 to 22 of the application as originally filed, which discloses a process for the preparation of a tablet comprising the steps (i) to (iii), which may further comprise a coating step (iv). The use of only non-aqueous solvents in the granulation and coating process, if mycophenolic acid and mycophenolate salt is anhydrous, is also disclosed in this context (see page 11, lines 18 to 24). The disclosure on page 11 does not specifically refer to enteric coating. However, the only type of coating that is explicitly and in detail disclosed in the application as originally filed is an enteric coating (see pages 7 to 10). Hence, the addition of the feature "enteric" does not add any technical information which is not directly and unambiguously derivable from the application as originally filed. The same applies with regard to the amount of mycophenolic acid or mycophenolate salt (i.e. 20 to 80%), which finds a basis on page 2, lines 27 to 31. This passage, which refers to a tablet, discloses an amount of 20 to 90% and a preferred amount of 45 to 80%. According to established jurisprudence a combination of the preferred disclosed narrower range and one of the part-ranges lying within the disclosed overall range on either side of the narrower range is unequivocally derivable from the original disclosure (see e.g. T 2/81, OJ EPO 1982, 394, point 2 of the headnote and point 3 first paragraph of the Reasons; T 925/98, point 2 of the Reasons, T 2001/10, point 10 of the Reasons).

Claims 2 to 5 find a basis on page 3, lines 20 to 24 and page 2, lines 27 to 31 of the application as originally filed.

- 2.3 The board therefore concludes that the subject-matter of the main request does not extend beyond the content of the application as originally filed. Article 123(2) EPC is therefore complied with.
3. Article 84 EPC
- 3.1 Claim 1 of the main request contains the expression "substantially anhydrous form". It has been argued by the third party that due to the term "substantially" said expression was unclear.
- 3.2 In decision G 3/14 (OJ EPO 2015, A102) of the Enlarged Board of Appeal, it was decided that "the claims of the patent may be examined for compliance with the requirements of Article 84 EPC only when, and then only to the extent that the amendment introduces non-compliance with Article 84 EPC" (see order).
- 3.3 The unclear term and the unclear expression were already present in the claims as granted. It was not argued, and the board has no reason to believe, that the alleged lack of clarity was introduced by any of the amendments made after the grant of the patent in suit. Rather, it was submitted that, in line with decision T 1459/05, an exception to the rule that there is no power to examine the amended claim under Article 84 EPC should be made. The board notes that the Enlarged Board of Appeal in its decision G 3/14 disapproved the line of diverging jurisprudence (see point 87 and points 30 to 43 of the Reasons), including decision T 1459/05.
- 3.4 In view of the above considerations, the board concurs with the appellants that the board has no power to

examine the clarity objection raised in the third party observation.

4. Sufficiency of disclosure and novelty

4.1 In the decision under appeal, the opposition division held that the subject-matter of all requests was sufficiently disclosed. Although the present main request is not identical to any of the requests underlying the decision under appeal, the board has no reason to deviate from the opposition division's findings. The same applies with regard to novelty.

5. Inventive step

5.1 The board, in agreement with the appellants, considers that document (1) represents the closest prior art. This document relates to enteric coated pharmaceutical compositions of mycophenolate salts (see claim 1). Suitable pharmaceutical compositions are tablets, pellets, granules or capsules. The enteric coating may be carried out in conventional manner, e.g. spraying with a solution. The solvents may be an organic solvent or an aqueous solution (see page 5, lines 5 to 13). The examples of document (1) disclose the preparation of enteric coated capsules by mixing mycophenolic mono sodium salt with suitable excipients, filling the mixture into a size 1 capsule and coating the capsule with a solution of the enteric coating ingredients in ethanol/acetone. The specific enteric coated capsules produced in examples 1 and 2 contain 16% mycophenolic acid mono sodium salts based on the total weight of the capsule contents and the enteric coating. A larger capsule with ten times the amount of salt is suggested, with a reduction of the amount of lactose (see page 11, lines 19 to 20). As this amount is not defined, no

conclusion as to the relative amount of mycophenolic acid salt can be drawn.

Document (1) does not place any emphasis on the use of anhydrous mycophenolic acid or mycophenolate salts. It does not mention such a form, although, according to a calculation made by the opposition division, which was accepted by the appellant, an anhydrous form has incidentally been used in the preparation of the capsules.

Document (1) also mentions that for mycophenolate salts the production of tablets is particularly interesting (see page 2, lines 21 to 25). However, no such tablet has been prepared and no details as to the preparation of tablets are provided.

- 5.2 In the light of document (1), the board sees the problem to be solved in the provision of a process for the production of an enteric coated tablet for oral administration of mycophenolic acid or its salts, which is convenient to administer.

The proposed solution is the production of such a tablet via direct compression (step (ii) is optional) or granulation and compression followed by enteric coating, which uses anhydrous mycophenolic acid or mycophenolate salts in an amount of 20 to 80% by weight based on the total weight of the enteric-coated tablet and carries out the granulation and coating step with non-aqueous solvents.

- 5.3 The board has no reason to doubt that the above formulated problem is solved.

- 5.4 It then remains to be decided, whether the claimed process was obvious for the person skilled in the art in view of the prior art.
- 5.5 It is undisputed that direct compression and wet granulation/compression (i.e. steps (i) to (iii)) are *per se* well-known methods in the preparation of tablets, with which the person skilled in the art is undoubtedly familiar (see document (10), page 1633, right-hand column, last paragraph, page 1634, section entitled "Compressed tablets", document (13), section 9.1, paragraph bridging the right- and left-hand column; document (14), page 70, lines 1 to 3 of first paragraph). The same applies to the coating step (see for example document (10), page 1634, left-hand column, first three paragraphs). The question to be examined is therefore whether the skilled person in an attempt to put the teaching of document (1) into practice and prepare tablets containing mycophenolic acid or mycophenolate salt as suggested in document (1) would have used the presently claimed amount of drug and the non-aqueous solvents in the coating and the granulation step.
- 5.6 Document (1) is silent as to the relative amount of mycophenolic acid or mycophenolate salts to be used in the pharmaceutical compositions (e.g. capsules, pellets, granules, tablets) disclosed therein. The only reliable information in this respect can be found in examples 1 and 2, in which this amount is 16%. The board also notes that none of documents (10), (13) or (14), which are considered to represent common general knowledge, addresses the issue of what would be a conventional or commonly used or achievable drug load in tablets prepared by direct compression or wet granulation and compression.



On page 8, lines 10 to 11, document (1) discloses that representative unit dosage forms contain from about "50 mg, e.g. 100 mg, to about 1.5 g" mycophenolate salt. There is no disclosure in this context as to the relative amount of the drug in the various unit dosage forms, let alone any reference to tablets.

5.7 It is also undisputed that the preparation of tablets usually requires the presence of excipients/additives to provide the necessary physical (and possibly chemical) characteristics of the material to be formulated into the tablet and of the tablets themselves. In the present case, the board concurs with the appellants that the preparation of an enteric coated tablet requires acceptable mechanical stability, otherwise the tablets are liable to crumble, edge, chip or break during coating. As acknowledged in the patent in suit (see paragraph [0009]), using a drug with e.g. a low bulk density, such as mycophenolic acid or mycophenolate salt, in high amounts has the disadvantage that high amounts of excipients are usually required to ensure sufficient mechanical stability of the tablet, which would result in a tablet with an undesirable or unacceptable size. Decreasing the amount of excipients leads to tablets with inferior mechanical stability which creates problems in the coating step.

In view of these difficulties and faced with the technical problem as formulated in point 5.2 above, the board concurs with the appellants that the skilled person had no incentive to increase the drug load taught in document (1) (i.e. 16%) when preparing the suggested enteric coated tablets by direct compression or wet granulation and compression.

5.8 Furthermore, as already explained in point 5.1 above, document (1) places no emphasis on the use of an anhydrous form of the mycophenolic acid or mycophenolate salt. It also does not teach the skilled person to avoid aqueous solutions in the coating and granulation step. On the contrary, aqueous solutions are mentioned as equally suitable for the coating step (see page 5, lines 7 to 13). No information regarding the granulation solvent can be found anywhere in document (1).

In the absence of any evidence to the contrary, the board accepts the appellants' argument that the anhydrous form was found to be the form best suited for the production of tablets and that it converts to hydrates as already indicated in the patent in suit (see paragraph [0055]), which jeopardises reproducible tablet production. This problem of conversion into hydrates has not been discussed in the available prior art. The skilled person had therefore no reason to avoid the use of aqueous solution during granulation and coating.

5.9 A number of prior art documents appear to suggest the use of high amounts of mycophenolic acid or mycophenolate salt in tablets (documents (2) to (4), (12) and (22)). However, none of them is concerned with the preparation of enteric coated tablets, which as explained in point 5.7 above requires adequate mechanical stability. Moreover, the disclosure in document (3) (see example 3, referring an active ingredient "e.g., mycophenolic acid, mycophenolate [*sic*] mofetil, or a pharmaceutically acceptable salt or derivative thereof") and document (22) ("up to 99% of the active ingredient", see page 15, lines 28 to 33) is

rather general and speculative. It does not prompt the skilled person to increase the drug load in enteric coated tablets as suggested in document (1), in particular taking into account the difficulties associated therewith. Document (4) is concerned with aqueous suspensions and documents (2) and (12) (see examples) disclose a wet granulation process, in which an aqueous maize paste in unknown quantities is used. Accordingly, none of these documents alone or in combination with the disclosure in document (1) would lead the skilled person in an obvious manner to the presently claimed process.

- 5.10 The same applies with regard to document (7). This document refers to a new enteric coated formulation of mycophenolic acid-sodium (ERL 080A). It states that "[A]n initial human relative bioavailability study (...) allowed the selection of an ERL 080A tablet strength of 360 mg for further development" and mentions in the last line that "Future clinical trials will utilize the enteric coated 360 mg ERL 080A tablet". It also mentions an oral dose of "ERL 080A 720 mg". Whether this oral dose was indeed a tablet is not clear. Document (7) is silent as to the relative amount of the drug in the tablet. However, even if, in view of the common general knowledge with regard to conventional tablet weights and sizes (see document (14), page 71, second paragraph), it were to be accepted that the use of an amount of 360 mg would result in tablet with an amount of mycophenolate salt within the claimed range, the board notes that document (7) is also silent as to how the tablet has been prepared, e.g. by direct compression, dry granulation/compression, wet granulation/compression or injection moulding (see document (5)). In particular,

there is no disclosure to avoid aqueous solutions during granulation and coating.

- 5.11 In view of the above, the board concludes that none of the available prior art documents, either alone or in combination leads the person skilled in the art in an obvious manner to a process according to claim 1 of the main request. The subject-matter of the main request therefore complies with Article 56 EPC.

## Order

### **For these reasons it is decided that:**

1. The decision is set aside.
2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of claims 1 to 5 submitted at the oral proceedings of 9 May 2017, and a description to be adapted thereto.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated