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**Datasheet for the decision
of 25 May 2018**

Case Number: T 2594/12 - 3.3.01
Application Number: 07850168.1
Publication Number: 2100610
IPC: A61K31/4365, A61K9/20, A61P7/02
Language of the proceedings: EN

Title of invention:

PHARMACEUTICAL COMPOSITION CONTAINING LOW-SUBSTITUTED
HYDROXYPROPYLCELLULOSE

Applicant:

Daiichi Sankyo Company, Limited
Ube Industries, Ltd.

Headword:

Tablets comprising prasugrel hydrochloride/DAIICHI UBE

Relevant legal provisions:

EPC Art. 123(2)
RPBA Art. 13(1)

Keyword:

Amendments - added subject-matter (yes)
Late-filed auxiliary request - justification for late filing
(no)

Decisions cited:

Catchword:



Beschwerdekammern
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Case Number: T 2594/12 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 May 2018

Appellant: Daiichi Sankyo Company, Limited
(Applicant 1) 3-5-1, Nihonbashi Honcho
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Appellant: Ube Industries, Ltd.
(Applicant 2) 1987-96, O-Aza Kogushi
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 11 July 2012
refusing European patent application No.
07850168.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: G. Seufert
C. Brandt

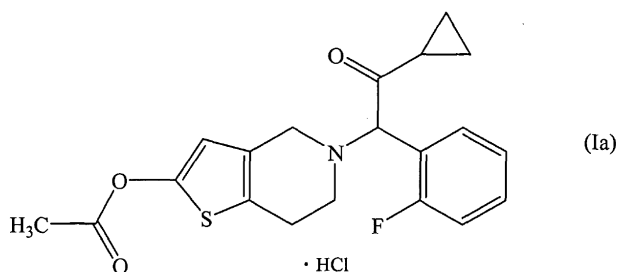
Summary of Facts and Submissions

- I. The applicants (appellants) lodged an appeal against the decision of the examining division refusing European patent application No. 07 850 168.1.
- II. The decision under appeal is based on sets of claims according to a main request and auxiliary requests 1 and 2, all submitted with letter dated 19 March 2012, and auxiliary request 3, submitted at the oral proceedings before the examining division.

The examining division held that the subject-matter of the main request and auxiliary requests 1 and 2 lacked an inventive step. Auxiliary request 3 was not admitted into the proceedings.

- III. With the statement of grounds of appeal, the appellants filed sets of claims according to a main request and a first auxiliary request. The main request was the same as auxiliary request 2 underlying the decision under appeal. Its sole claim reads as follows:

"1. A pharmaceutical composition in the form of a tablet, the tablet consisting of:
a compound represented by the following formula (Ia):



hydroxypropyl cellulose;
lactose;

magnesium stearate; and
a low-substituted hydroxypropyl cellulose."

The sole claim of the first auxiliary request differs from the main request in that the low-substituted hydroxypropyl cellulose is present **"in an amount of 10.0 to 30.0% by weight with respect to the total amount of the pharmaceutical composition"**.

- IV. In a communication issued in preparation of the oral proceedings, the board indicated, *inter alia*, that it had concerns as to the compliance of the appellants' requests with Article 123(2) EPC.
- V. At the oral proceedings, the appellants filed auxiliary request A, which differs from the main request in that the expression "the tablet consisting of:" has been replaced by the expression **"the tablet comprising:"**
- VI. The appellants' arguments, as far as they concern the issues which are decisive for the present decision, can be summarised as follows.

- Amendments (Article 123(2) EPC)

The claimed subject-matter complied with Article 123(2) EPC. The amendments were based on the examples in combination with the general part of the description.

The examples contained exclusively the presently claimed ingredients. The difference between examples 1 and 2 was merely the higher amount of low-substituted hydroxypropyl cellulose and the reduced amount of lactose in example 2, which showed that the amounts of the ingredients could be varied.

The skilled person was also told in the general part of the description of the application as originally filed that in addition to the low-substituted hydroxypropyl cellulose further additives could be present (see page 6, lines 19 to 23). For each class of these additives (e.g. fillers, lubricants, binders) preferred embodiments were mentioned, for example lactose as filler (see page 7, lines 1 to 2), magnesium stearate as lubricant (see page 7, lines 4 to 5), and hydroxypropyl cellulose as binder (see page 7, lines 16 to 17). Tablets were mentioned as a preferred form of the disclosed pharmaceutical compositions (see page 8, line 25) and a compound of formula (Ia) was a preferred form of the active ingredient (see page 4, penultimate paragraph). Low-substituted hydroxypropyl cellulose was the key feature of the invention and was mentioned throughout the application. The inventive effect was demonstrated by the examples, which clearly represented embodiments of the invention. Taken together with the general disclosure they provided a proper basis for the presently claimed subject-matter. The invention was not altered thereby and the skilled person was not provided with any information that he was not aware of from the application as a whole.

It was not disputed that the amount of low-substituted hydroxypropyl cellulose had an influence on the dissolution rate. It was also not disputed that the other ingredients would, to some extent, also alter the properties of the tablet. However, this did not change the nature of the invention, according to which the effect was due to the presence of low-substituted hydroxypropyl cellulose.

Concerning the manufacturing process, the skilled person was taught that the direct compression method

was preferred. It was expected that the use of other manufacturing methods would result in a tablet with the same advantageous properties regarding dissolution rates and disintegration time.

The same arguments applied with respect to the subject-matter of claim 1 of the first auxiliary request, which differed only in the amount of low-substituted hydroxypropyl cellulose. A basis for this amendment could be found on page 8, line 11 of the application as filed. The amount of low-substituted hydroxypropyl cellulose in the examples fell within that range.

- Admission of auxiliary request A

This request was filed in response to the discussion that took place at the oral proceedings before the board. The amendment addressed the board's objection concerning the exclusivity of the claimed list of ingredients and was supported by the disclosure on page 6.

VII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims according to the main request, or, alternatively on the basis of the set of claims according to the first auxiliary request, both filed with the statement of grounds of appeal, or on the basis of auxiliary request A filed during the oral proceedings.

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

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Amendments (Article 123(2) EPC)

- 2.1 The application as originally filed relates in general to a pharmaceutical composition comprising a compound of formula (I) (hereinafter prasugrel) or a pharmacologically acceptable salt thereof and a low-substituted hydroxypropyl cellulose (see claims 1). According to claim 5 as originally filed, the compound according to formula (I) is prasugrel hydrochloride (formula (Ia)). According to claim 8 the pharmaceutical composition is in the form of a tablet. The same disclosure is present in the general description of the application as filed (see page 3, line 16 to page 5, line 6). A variety of other ingredients such as fillers, lubricants, binders, emulsifiers, stabilisers, corrigents and/or diluents may be present in the pharmaceutical compositions (see page 6, lines 19 to 23). Detailed information is provided for each of these potential ingredients on page 6, line 24 to page 7, penultimate line. Several preferred alternatives are mentioned for the fillers (i.e. lactose and/or crystalline cellulose), lubricants (i.e. calcium or magnesium stearate) and binders (i.e. hydroxypropyl cellulose, hydroxypropylmethyl cellulose; see page 7, lines 1 to 2, 3 to 5 and 16 to 17). On page 8, lines 18 to 25, it is disclosed that the pharmaceutical composition is preferably in the form of a solid preparation. Reference is made to tablets as the most preferred form. No ingredients are specified in this context.

2.2 Compared to claim 1 of the application as originally filed, claim 1 of the main request has been amended by specifying that the pharmaceutical composition is a tablet consisting of prasugrel hydrochloride, hydroxypropyl cellulose, lactose, magnesium stearate and a low-substituted hydroxypropyl cellulose.

2.3 According to the appellants, the subject-matter of claim 1 of the main request was based on the examples 1 and 2 taking into account the preferred features disclosed on page 7, lines 1 to 2, 4 to 5 and 16 to 17, and page 8, line 18.

2.4 The board concurs with the appellant that examples 1 and 2 indeed disclose tablets containing solely the ingredients according to claim 1 of the main request. In fact, the examples are the only part of the application as originally filed where such tablets are disclosed. However, in these examples the specific ingredients are also present in specific amounts, and the tablets are the product of a particular process.

In example 1 prasugrel hydrochloride (32.9 g), low-substituted hydroxypropyl cellulose (24 g), hydroxypropyl cellulose (12 g), lactose (168.7 g) and magnesium stearate (2.4 g) had been mixed with a high-intensity mixture to give a mixed powder, which was subsequently compressed using a rotatory tableting machine with a tableting pressure of 5.9 kN so that the tablet mass became 80 mg. Example 2 differs from example 1 solely in that the amount of low-substituted hydroxypropyl cellulose had been increased to 48 g and the amount of lactose had been reduced to 144.7 g.

2.5 It is also shown in the application as originally filed that the tablets of examples 1 and 2 exhibit excellent

disintegration properties and dissolution rates for compound A, which is the intended goal of the invention (see page 14, lines 5 to 25, tables 1 and 2 on pages 14 and 15). Compound A is prasugrel hydrochloride (see page 12, second paragraph).

- 2.6 However, the disintegration and dissolution tests reported in tables 1 and 2 are related to the tablets of examples 1 and 2 as a whole, in which the specific ingredients in the therein defined amounts contribute together to the properties of the tablets. It is self-evident for any skilled person that the inherent physico-chemical properties of each tablet ingredient, for example its hydrophilicity, hydrophobicity, viscosity etc., and the respective amount (absolute and relative) in which it is present will have an impact on the properties of the tablet and, consequently, the dissolution rate of the active ingredient(s). The appellants' argument that the observed effects in examples 1 and 2 were solely due to the low-substituted hydroxypropyl cellulose, independent of the nature and the amount of any of the other ingredients, is therefore not accepted.

Furthermore, the properties of a tablet are also influenced by the manufacturing process of the tablet, i.e. whether the ingredients are simply mixed and compressed with a particular compaction force as in examples 1 and 2, or whether granulation, particle size regulation and/or coating steps are included as disclosed on pages 9/10 of the application as originally filed. In this context, the board observes that hydroxypropyl cellulose does not only work as a binder but is also used as a coating base agent (see application, page 10, line 21).

2.7 Thus, in the board's judgement, the person skilled in the art derives from examples 1 and 2 nothing more than the bare disclosure that excellent disintegration times for the tablet and dissolution rates for prasugrel hydrochloride are achieved, if certain conditions are fulfilled, i.e. if specific additives in certain amounts are present and the tablet is prepared in a particular way.

2.8 The board does not dispute that the skilled person will be aware that it is possible to vary the examples to a limited extent. Indeed as pointed out by the appellant a comparison between examples 1 and 2 shows that an increase in low-substituted hydroxypropyl cellulose, which is known in the art as a disintegrant, and a simultaneous reduction in lactose, which according to the application as filed works as a filler and a binder (see paragraph bridging pages 6 and 7 and page 7, lines 13 to 16), have an influence on the dissolution rate of prasugrel hydrochloride, if the other ingredients (i.e. the active ingredient, hydroxypropyl cellulose, which can act as a binder, and magnesium stearate which is a known lubricant and emulsifying agent) remain constant. However, no conclusion can be drawn from the examples as to within what limits such variation will be possible. In particular, it is not clearly and unambiguously recognisable from the two specific examples that if the tablet is to be limited to those ingredients mentioned in these examples, the amounts in which they are present can be freely chosen whilst substantially the same results (i.e. excellent disintegration time of the tablet and dissolution rate of prasugrel hydrochloride) would be achieved. The two specific tablets cannot therefore be used as a basis for the subject-matter of claim 1 of the main request which covers tablets consisting of the claimed

ingredients in any amount or being produced by any process.

Nor can such a basis be found anywhere else in the application as originally filed. The general part of the description and the claims place no restriction on the number or the identity of specific ingredients. Moreover, the description offers several preferred alternatives for certain ingredients, which may or may not be present (see point 2.1 above). A tablet consisting of prasugrel hydrochloride, hydroxypropyl cellulose, lactose, magnesium stearate and low-substituted hydroxypropyl cellulose, is not disclosed, either in the claims or the general part of the description as originally filed.

2.9 It follows from the above that the presently claimed tablet with its closed list of specific ingredients in undefined amounts, although encompassed by the generic disclosure of the invention, has no directly and unambiguously derivable basis in the application as filed. The appellants' argument that the skilled person is not presented with new technical information is therefore not accepted.

2.10 Hence, the board concludes that the subject-matter of claim 1 of the main request contravenes Article 123(2) EPC.

Auxiliary request

3. Amendments (Article 123(2) EPC)

3.1 Claim 1 of the auxiliary request differs from claim 1 of the main request in that the amount of low-substituted hydroxypropyl cellulose has been limited to

an amount of 10.0 to 30.0 % by weight with respect to the total amount of the pharmaceutical composition (i.e. the tablet).

3.2 The feature as such has a basis in the application as originally filed (see page 8, line 11). However, this amendment does not alter the above assessment of non-compliance with Article 123(2) EPC. A tablet consisting of prasugrel hydrochloride, hydroxypropyl cellulose, lactose, magnesium stearate and low-substituted hydroxypropyl cellulose in which only the amount of low-substituted hydroxypropyl cellulose is specified has no clear and unambiguous basis in the application as filed.

3.3 The same observations and the same conclusion as in points 2.5 to 2.10 above apply, with the consequence that the auxiliary request must also be refused for contravening Article 123(2) EPC.

Auxiliary request A

4. Admission into the proceedings

4.1 Auxiliary request A has been filed at a very late stage of the proceedings, namely after the board had announced its conclusion that the main request contravened Article 123(2) EPC. The filing of this request constitutes an amendment to the appellants' case pursuant to Article 13(1) RPBA. Under this article, the admission of late filed requests are left to the discretion of the board.

4.2 According to established jurisprudence of the boards of appeal, one of the criteria which may be decisive for the admission of a late-filed request are whether good

reasons existed for its late filing, as may be the case where amendments are occasioned by developments during the proceedings.

- 4.3 The appellants justified the late-filing of auxiliary request A as a direct reaction to the preceding discussion and an attempt to overcome the board's objections with regard to the exclusive list of ingredients.
- 4.4 However, the board has already expressed its concerns regarding compliance with Article 123(2) EPC in its communication of 2 March 2018. No new issues were raised at the oral proceedings. The discussion focused on the question whether the examples provided a proper basis for the claimed subject-matter as indicated in the board's communication of 2 March 2018 (see point 4.2). Hence, the appellants could and should have filed a request with appropriate amendments at an earlier stage in the appeal proceedings. No good reasons existed for them to wait until the board had announced its conclusion. The appellants' arguments that the filing was a timely and appropriate reaction to the course of the oral proceedings is therefore not accepted. Furthermore, the board notes that it still considers it doubtful whether the subject-matter of auxiliary request A had a clear and unambiguous basis in the application as filed.
- 4.5 Hence, the board, making use of its discretionary power pursuant to Article 13(1) RPBA, decided not to admit auxiliary request A into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated