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Datasheet for the decision of 25 May 2018

Case Number: T 2596/12 - 3.3.01

Application Number: 07850164.0

Publication Number: 2100607

IPC: A61K31/4365, A61K9/20, A61P7/02

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION HAVING IMPROVED STORAGE STABILITY

Applicant:
Daiichi Sankyo Company, Limited
Ube Industries, Ltd.

Headword:
Prasugrel tablets comprising hydroxypropyl cellulose/DAIICHI UBE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no) - improvement not credible - obvious alternative

Decisions cited:
T 0181/82

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2596/12 - 3.3.01

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

Appellant: (Applicant 1)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi Honcho Chuo-ku Tokyo 103-8426 (JP)
Appellant: (Applicant 2)	Ube Industries, Ltd. 1978-96, Oaza Kogushi Ube City, Yamaguchi 755-8633 (JP)
Representative:	Fairbairn, Angus Chisholm Marks & Clerk LLP 90 Long Acre London WC2E 9RA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 July 2012 refusing European patent application No. 07850164.0 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 the European patent application No. 07 850 164.0.

II. The present decision refers to the following documents:

D1 EP-A-1298132

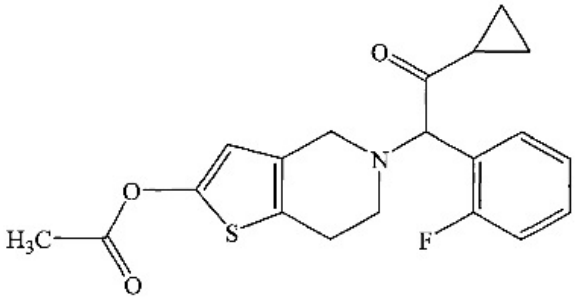
III. The decision under appeal was based on a main request and auxiliary requests 1 to 3, all filed with letter of 19 March 2012.

The examining division considered that the subject-matter of claims 1 and 2 of the main request and auxiliary request 1 did not involve an inventive step in view of document D1. Claims 1 of auxiliary requests 2 and 3 were considered to contravene Article 123(2) EPC.

IV. With the statement setting out the grounds of appeal, the appellants filed sets of claims according to a main request and first and second auxiliary requests.

The main request contains two claims with claim 1 reading as follows:

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



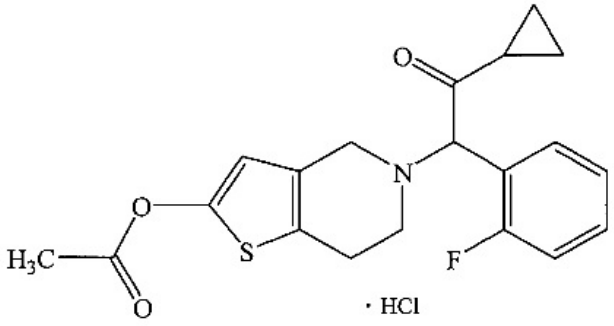
(I)

or a pharmacologically acceptable salt thereof; and
(B) a water-soluble polymer, wherein the water-soluble polymer is hydroxypropyl cellulose,
which tablet may be provided with at least one layer of a film-coating."

Claim 1 of the first auxiliary request differs from claim 1 of the main request in that hydroxypropyl cellulose is present **"in an amount of 2.5 to 20.0% by weight with respect to the total amount of the composition of the tablet"**.

The second auxiliary request consists of a single claim, which 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):



(Ia)

a disintegrant;
lactose;
magnesium stearate; and
a water-soluble polymer, wherein the water-soluble polymer is hydroxypropyl cellulose,
which tablet may be provided with at least one layer of a film-coating.

V. In a communication issued in preparation of the oral proceedings, the board expressed its preliminary opinion. It was indicated, *inter alia*, that the board had doubts as to whether the technical effect on which the appellants relied had been properly demonstrated. In the absence of such an effect, the board was inclined to agree with the examining division that the claimed subject-matter lacked an inventive over the teaching of document D1.

VI. The appellants' arguments, as far as they concern the issues which are decisive for the present decision, can be summarised as follows:

Document D1 could be considered as the closest prior art. It disclosed tablet formulations comprising a prasugrel salt as active ingredient and mentioned the possibility of including binders (such as hydroxypropyl cellulose), fillers or excipients (such as lactose), lubricants (such as magnesium stearate) and disintegrants (such as sodium croscarmellose) (see D1, paragraphs [0020] to [0025]. It also disclosed specific tablets (see formulation examples 2 and 4), in which lactose, known to be a binder and a filler, and, admittedly, cellulose functioned as binder.

The problem to be solved by the presently claimed subject-matter was the provision of a tablet

formulation with improved storage stability. This was achieved by the presence of hydroxypropyl cellulose.

The improved storage stability was demonstrated by the results shown in table 1 of the application, in particular the comparison between example 1 and comparative example 1. In example 1 hydroxypropyl cellulose and, to some extent, lactose functioned as binder. In comparative example 1 lactose to some extent functioned as binder. Both example 1 and comparative example 1 contained the same amount of material constituting the binder. Comparing the storage stability of example 1 and comparative example 1 showed that using hydroxypropyl cellulose as specific binder component in the tablet formulation significantly improved the storage stability (active ingredient remaining: 73% vs 4%). This effect could be attributed solely to the presence of hydroxypropyl cellulose, since the respective formulations used in the comparison were identical except that in example 1 some of the lactose had been replaced by hydroxypropyl cellulose. The only difference was the presence of hydroxypropyl cellulose.

A comparison against tablets using any of the other binders mentioned in document D1 was not necessary. This document disclosed that binders might be chosen from a list of known binders (see paragraph [0024]), but did not teach or recommend the use of any specific binder from that list. Accordingly, the comparison made against a tablet which contained "a binder" as in comparative example 1 was a valid and sufficient comparison with the closest prior art.

Even if it had to be acknowledged that there was no exact comparison with the prior art, the effect had at least been made plausible.

The observed technical effect was unexpected and not derivable from document D1. This document was mainly directed to prasugrel salts. It was not concerned with storage stability. No emphasis was placed on the presence of any particular additive (i.e. excipients, fillers, binders etc.) and none of them was singled out as particularly required. At best, document D1 taught the use of unspecified binders in formulations comprising prasugrel. Binders were normally included in tablets to improve cohesion and mechanical strength. It was surprising and entirely unexpected that a specific binder (i.e. hydroxypropyl cellulose) would also improve storage stability. The claimed subject-matter was therefore not obvious for the skilled person in view of the prior art.

The arguments submitted for the main request applied also to first and second auxiliary requests. Moreover, document D1 did not disclose or suggest the amount of hydroxypropyl cellulose according to claim 1 of the first auxiliary request. The subject-matter of claim 1 of the second auxiliary request was closely related to example 1 of the application, for which the technical effect of improved storage stability had been shown. Furthermore, the tablets according to document D1 did not contain a disintegrant. The technical effect, however, was not based on the presence of a disintegrant.

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 or second auxiliary requests, all filed with the statement of grounds of appeal.

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. Inventive step (Article 56 EPC)

2.1 Claim 1 of the main request is directed to a tablet comprising a compound of formula (I) (hereinafter prasugrel) and hydroxypropyl cellulose (see point IV above).

2.2 The board considers, in agreement with the examining division and the appellants, that document D1 is a suitable starting point for the assessment of inventive step.

This document discloses prasugrel salts and pharmaceutical formulations comprising them. The formulations may be, *inter alia*, in the form of tablets (see D1, paragraph [0020]). Additives, such as excipients, lubricants, binders, disintegrants, emulsifiers, etc., may be present in the formulations (see D1, paragraph [0021]). Excipients include, *inter alia*, sugar derivatives, such as lactose, sucrose, starch derivatives, such as corn starch potato starch, cellulose derivatives, such as crystalline cellulose

(see D1, paragraph [0022]). Binders to be used include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone or excipients as described in paragraph [0022] (see D1, paragraphs [0024]).

Document D1 also explicitly discloses tablets with prasugrel hydrochloride or maleate, cellulose, lactose and magnesium stearate as ingredients (see page 10, formulation examples 2 and 4).

According to the board's knowledge, cellulose is commonly known to have binding properties. That has been conceded by the appellants at the oral proceedings before the board and confirms the appellants' view expressed in the statement of grounds of appeal (see point 8, last two lines). Lactose, although mainly used as filler, is also known to be useful as a binder. That has been acknowledged by the appellants in the statement of grounds of appeal (see page 4, point 4). Magnesium stearate acts as lubricant.

2.3 In the light of document D1, the appellants defined the problem to be solved as the provision of a tablet with improved storage stability.

2.4 The proposed solution lies in the presence of hydroxypropyl cellulose.

2.5 In order to demonstrate that the technical problem as defined above has effectively been solved, the appellants relied on results provided in the application, in particular the comparison between example 1 and comparative example 1.

2.6 In example 1 of the application prasugrel hydrochloride (3.4 g), hydroxypropyl cellulose (17.5 g),

croscarmellose sodium (12.5 g), lactose (215.3 g) and magnesium stearate (1.3 g) had been mixed to give a powder, which was compressed to obtain tablets of approximately 80 mg. Hydroxypropyl cellulose and lactose constitute the binder. In a subsequent step the tablets were coated. In comparative example 1 lactose alone, the amount of which had been increased by 17.5 g, constitutes the binder. Stability tests with example 1 and comparative example 1 showed an improved storage stability for example 1 (73% vs 4%; see application page 15, table 1).

It is immediately apparent that the comparative example of the application does not reflect the closest state of the art, namely the tablets disclosed in document D1, in which cellulose and lactose constitute the binder.

2.7 The appellants argued that the comparison made was a fair comparison. Example 1 and comparative example 1 differed only in the presence of hydroxypropyl cellulose. Therefore, the observed improvement in storage stability could clearly be attributed to the presence of hydroxypropyl cellulose. The effect was highly surprising for a binder, the purpose of which was normally to improve the mechanical strength of a tablet. Moreover, document D1 disclosed that binders might be chosen from a list of known binders (see D1, paragraph [0024]). No specific binder from that list was taught or recommended. Therefore, the comparison made against a tablet which contained "a binder" (i.e. lactose as in comparative example 1) was a valid comparison with the prior art.

2.8 The board does not agree.

It cannot be denied that an improvement in storage stability has been observed for example 1 compared to comparative example 1. However, comparative example 1 does not reflect the closest state of the art (i.e. the tablets according formulation examples 2 and 4). The comparison against this example is therefore not suitable for making the alleged improvement in storage stability plausible, let alone surprising. The board also notes that it is established jurisprudence of the boards of appeal that where comparative tests were relied on as evidence for an alleged effect, there must be the closest possible structural approximation to the subject-matter of the invention (see T 181/82, OJ EPC 1984 401, headnote I). This is not the case here. The selection of lactose as a binder in comparative example 1 does not represent the closest approximation, because other binders, such as cellulose derivatives (e.g. microcrystalline cellulose), which are structurally much closer to the claimed hydroxypropyl cellulose than lactose, are equally suggested in paragraph [0024] of document D1. Moreover, the use of cellulose has been explicitly taught in formulation examples 2 and 4 of document D1. Hence, in the board's judgement, for a proper comparison it would have been necessary to compare the tablet according to example 1 of the application comprising hydroxypropyl cellulose and lactose against a tablet comprising cellulose and lactose as in the formulation examples 2 and 4 of document D1. The board also notes that lactose and cellulose, although both are useful as binders, belong to different classes of compounds with different physico-chemical properties. Any effect that may have been shown against lactose cannot be extrapolated to cellulose.

2.9 It follows from the above that the comparison of example 1 of the application with comparative example 1 cannot properly demonstrate that the purported improvement in storage stability of the claimed tablet has been successfully achieved vis-à-vis the tablets known from document D1. Accordingly, the technical problem as defined by the appellant (see point 2.3 above) needs to be reformulated in a less ambitious way. In the light of document D1, the board considers that the problem to be solved was the provision of a further prasugrel comprising tablet. The board has no doubts that this problem has been solved by the claimed subject-matter.

2.10 It then remains to be decided whether the proposed solution is obvious for the skilled person in view of the prior art.

Document D1 discloses in the general part of the description that the prasugrel salt comprising pharmaceutical formulations can be prepared by well-known methods using additives, such as excipients, lubricants, binders, disintegrants, emulsifiers, etc. (see page 4, paragraph [0021]). Hydroxypropyl cellulose is explicitly disclosed as an example of a suitable binder (see page 4, paragraph [0024]). Its selection has not been shown to result in a particular technical effect and is therefore neither critical nor purposive. It is merely an arbitrary selection of no technical significance, made within the ambit of document D1. Such a selection does not require any inventive ingenuity. The claimed subject-matter is therefore obvious in view of the teaching of document D1 alone.

2.11 The appellants' arguments with regard to obviousness were based on the assumption that the purported

improvement in storage stability had been adequately established and was highly surprising (see point VI above).

2.12 However, since the objective technical problem consists merely in the provision of a further tablet, the appellants' arguments cannot succeed. As explained in point 2.10 above, the mere arbitrary selection of a binder, which is a commonly used additive in tablets, does not require inventive skills.

2.13 The argument that document D1 did not place any emphasis on any of the additives mentioned on page 4 and did not single out a particular additive can also not succeed. In the present case, where the technical problem is merely the provision of a further tablet and where the solution merely consists in arbitrarily selecting a feature within the ambit of document D1, no particular incentive for the selection is required.

2.14 For the aforementioned reasons, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

First auxiliary request

3. Inventive step (Article 56 EPC)

3.1 Claim 1 of the first auxiliary request differs from claim 1 of the main request in that the amount of hydroxypropyl cellulose is specifically defined (i.e. 2.5 to 20% by weight with respect to the total amount of the composition of the tablet).

3.2 This amendment does not alter the above assessment of inventive step regarding the subject-matter of the main

request. No advantageous effects or improvements have been shown to be associated with the selected amount. The problem to be solved therefore remains the same as formulated in point 2.9 above.

3.3 The selection of an appropriate amount of binder is a routine task which does not exceed the ordinary skills of the person skilled in the art. Inventive ingenuity is not required. Nor have the appellants provided any arguments - and none are apparent to the board - that the selected amount of hydroxypropyl cellulose would be unusual for a tablet binder.

3.4 For the aforementioned reasons, the board concludes that the subject-matter of claim 1 of the first auxiliary request also lacks an inventive step (Article 56 EPC).

Second auxiliary request

4. Inventive step (Article 56 EPC)

4.1 The sole claim of the second auxiliary request differs from the main request in that the tablet consists of a specific ingredients (i.e. prasugrel hydrochloride, a disintegrant, lactose, magnesium stearate and hydroxypropyl cellulose).

4.2 The tablet disclosed in formulation example 2 of document D1, which consists of prasugrel hydrochloride, lactose, magnesium stearate and cellulose, is considered to represent the closest state of the art.

4.3 At the oral proceedings before the board, the appellants admitted that no causal link existed between the allegedly observed improved storage stability and

the presence of a disintegrant. According to the appellants, this effect was associated with the presence of hydroxypropyl cellulose.

4.4 However, as explained in point 2.8 above, the purported improvement in storage stability has not been adequately demonstrated. Therefore, the objective technical problem is still considered to be the same as defined in point 2.9 above.

4.5 The selection of hydroxypropyl cellulose as binder or binder component does not require inventive skills for the reasons set out in point 2.10 above. The use of disintegrants is also explicitly suggested in document D1 (see paragraph [0021]). Its presence has admittedly not been shown to result in a particular technical effect and is therefore neither critical nor purposive. It is merely an arbitrary selection of no technical significance, made within the ambit of document D1, and as such does not require inventive skills.

4.6 For the aforementioned reasons, the second request must also be rejected for lack of inventive step of the claimed subject-matter (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Kiehl A. Lindner

Decision electronically authenticated