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**Datasheet for the decision
of 26 July 2018**

Case Number: T 1061/13 - 3.3.01

Application Number: 07850166.5

Publication Number: 2100609

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

Language of the proceedings: EN

Title of invention:

SOLID MEDICINAL PREPARATION CONTAINING MANNITOL OR LACTOSE

Applicants:

Daiichi Sankyo Company, Limited
Ube Industries, Ltd.

Headword:

Tablet uniformity/DAIICHI

Relevant legal provisions:

EPC Art. 56

Keyword:

Decisions cited:

Catchword:



Beschwerdekammern
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Case Number: T 1061/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 26 July 2018

Appellants:
(Applicants 1)

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted on
15 November 2012 refusing European patent
application No. 07850166.5 pursuant to Article
97(2) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: J. Molina de Alba
M. Blasi

Summary of Facts and Submissions

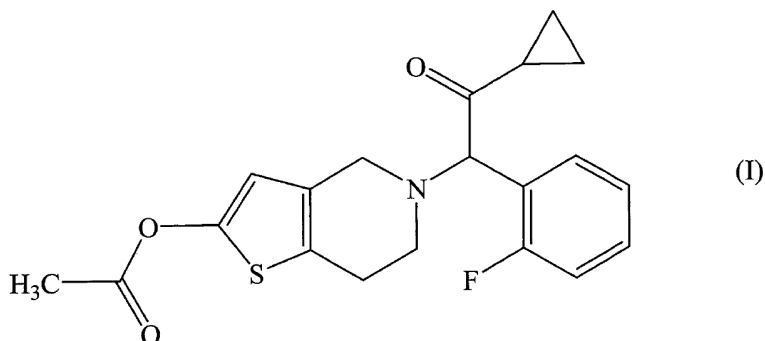
- I. The present appeal lies from the decision of the examining division refusing European patent application No. 07 850 166.5. The decision was based on a main request and three auxiliary requests.
- II. The documents cited in the course of the examination and appeal proceedings include the following:
- (1) EP-A-1298132
 - (2) JP-A-2003 246735
 - (3) JP-A-10 310586
 - (4) EP-A-1350511
 - (5) EP-A-1555032
 - (7) WO 2004/098713
 - (9) H. Larhrib et al., *International Journal of Pharmaceutics*, 191, 1999, 1-14
 - (10) M.P. Flament et al., *International Journal of Pharmaceutics*, 275, 2004, 201-209
 - (11) H. Schiavone et al., *International Journal of Pharmaceutics*, 281, 2004, 55-66
 - (12) M.M. He et al., *Pharmazeutische Industrie*, 57(11), 1995, 945-949

- III. In the present decision, the compound of formula (I) in the refused application is also referred to by its generic name "prasugrel". Similarly, the particle size distribution with a 90% cumulative diameter referred to in claim 1 of all requests is abbreviated to "D₉₀".
- IV. In its decision, the examining division found that the tablets in claim 1 of all requests lacked an inventive step starting from any of documents (1) to (5) and (7). The claimed tablets differed from the ones in the closest prior art in that their mannitol or lactose particles had a selected size distribution of D₉₀= 150-300 µm. The examining division held that, contrary to the applicants' opinion, the problem to be solved could not be formulated on the basis of an improvement in drug uniformity, because the improvement shown in table 1 of the application could not be exclusively ascribed to the selected D₉₀ defined in claim 1. This derived from the fact that the particles compared in table 1 differed not only in their D₉₀ but also in their type (spray-dried, granulated and agglomerated). As a result, the problem had to be reformulated less ambitiously, which then made the D₉₀ proposed in claim 1 of all requests an obvious selection.
- V. With the statement of grounds of appeal, the appellants (applicants) submitted three sets of claims as their main request and auxiliary requests 1 and 2.

Claim 1 of the main request reads as follows:

"1. A solid medicinal preparation in the form of a tablet comprising:

(A) a compound represented by the following general formula (I):



or a pharmacologically acceptable salt thereof; and

(B) mannitol or lactose which, when measured under the following conditions, has a particle size distribution in which the 90% cumulative diameter is 150 to 300 μm

(Measurement Conditions)

Particle size dispersion analyzer: HELOS (HI326) & RODOS System (manufactured by Sympatec GmbH);

Measurement range of laser diffraction unit: 0.5 to 875 μm ;

Calculation mode of laser diffraction unit:

Fraunhofer HRLD (v3.2 Rel.2);

Dispersing apparatus: RODOS Dry Dispersion System;

Dispersing pressure: 2.00 bar;

Vacuum degree: 100.00 mbar."

Claim 1 of auxiliary request 1 is based on claim 1 of the main request, but the amounts of components (A) and (B) and the new components (C) and (D) have been introduced and specified as follows (wt.% refers to the total weight of the solid medicinal preparation):

(A) 1.0 to 30.0 wt.%;

(B) 10.0 to 93.5 wt.%;

(C) 0.5 to 5.0 wt.% lubricant; and

(D) 0.0 to 15.0 wt.% binder.

Claim 1 of auxiliary request 2 is based on claim 1 of auxiliary request 1, but component (A) has been restricted to prasugrel **hydrochloride** and the concentration ranges of components (A) to (D) have been further limited to:

- (A) 1.3 to 20.0 wt.%;
- (B) 44.0 to 90.0 wt.%;
- (C) 0.5 to 3.0 wt.%; and
- (D) 2.5 to 10.0 wt.%.

The claims of the main request and auxiliary requests 1 and 2 correspond essentially to those of the main request and auxiliary requests 2 and 3 underlying the appealed decision, respectively.

- VI. Anonymous third-party observations were filed and transmitted to the appellants for information.
- VII. In its preliminary opinion, annexed to the summons to oral proceedings, the board concurred with the examining division that the tablets in claim 1 of all requests lacked an inventive step.
- VIII. Oral proceedings were held before the board on 26 July 2018.
- IX. The appellants' arguments, where relevant to the present decision, may be summarised as follows:

In their analysis of inventive step, the appellants concurred with the examining division that the closest prior art was any of documents (1) to (5) and (7). The tablets in claim 1 of the main request differed from the ones in the closest prior art in that they

contained lactose or mannitol particles with a size distribution of $D_{90} = 150-300 \mu\text{m}$, while documents (1) to (5) and (7) did not provide any information on the particle size of lactose or mannitol. The selected D_{90} in claim 1 resulted in tablets with improved drug uniformity. This had been shown in table 1 of the application, where the tablets according to the invention (examples 1 to 5) demonstrated the trend that the larger the D_{90} , the worse the drug content uniformity in the tablets. Table 1 also showed that this effect was independent of the type of lactose or mannitol particles. Hence, the application proved the correlation existing between D_{90} and drug content uniformity and plausibly showed that the claimed range of $D_{90} = 150-300 \mu\text{m}$ resulted in prasugrel tablets with improved drug content uniformity. In addition, even if only particles of the same type were considered, a comparison between example 4 and comparative example 1, both of which contained spray-dried mannitol particles, confirmed the effect and showed it to be plausible across the whole range of D_{90} disclosed in claim 1. Therefore, as the prior-art documents did not suggest the claimed D_{90} for improving drug content uniformity, the tablets in claim 1 of the main request were inventive.

With respect to the tablets in claim 1 of auxiliary requests 1 and 2, the appellants explained that the additional limitations rendered the achievement of a higher drug content uniformity even more credible.

- X. The appellants' final requests were that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or, alternatively, of one of auxiliary requests 1 and 2, all filed with the statement of grounds of appeal.

XI. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.
2. *Inventive step - claim 1 of the main request*
 - 2.1 The application in hand is directed to prasugrel tablets with excellent drug content uniformity. The tablets are characterised by the fact that they contain as a carrier mannitol or lactose particles with a size distribution of $D_{90} = 150-300 \mu\text{m}$.
 - 2.2 The appellants and the examining division concurred that any of documents (1) to (5) and (7) may be considered the closest state of the art because they all disclose prasugrel tablets containing lactose or mannitol particles as carrier. They concurred likewise that the tablets in claim 1 of the main request differ from the ones in the closest prior art in that the lactose or mannitol particles have a $D_{90} = 150-300 \mu\text{m}$, while documents (1) to (5) and (7) do not provide any information on the size of the lactose or mannitol particles.

The board agrees with those findings.
 - 2.3 The main point of dispute between the appellants and the examining division was the formulation of the technical problem solved by the tablets in claim 1.

This disagreement arises from their diverging conclusions regarding the experimental results presented in table 1 of the application. Thus, while the appellants concluded that the technical problem solved was the provision of prasugrel tablets with improved drug content uniformity, the examining division considered that the problem had to be reformulated less ambitiously.

The board therefore needs to investigate whether or not, in view of the examples in the application, the selection of lactose or mannitol particles having a $D_{90} = 150-300 \mu\text{m}$ effectively results in tablets with improved drug content uniformity and, if so, whether this improvement can be expected to be present across the whole breadth of claim 1.

- 2.4 The application contains five examples of tablets according to the invention and three comparative examples.

On these examples, the appellants noted (see point 7 of the statement of grounds of appeal) that the lactose-containing tablets in examples 1, 2, 3 and 5 and comparative example 2 have an identical chemical composition. Likewise, the mannitol-containing tablets in example 4 and comparative example 1 have an identical chemical composition. By contrast, the appellants conceded at the oral proceedings before the board that the composition of the tablets in comparative example 3 was different to that of the other examples and did not allow for comparison.

In this context, the examining division observed that the commercial particles in examples 1 and 5 were granulated, those in examples 2, 3 and 4 and

comparative example 1 spray-dried, and those in comparative example 2 agglomerated. This finding was not disputed by the appellants.

Thus, in line with the table on page 4 of the statement of grounds of appeal, the experimental evidence provided in the application may be summarised as follows (as in the application, RSD stands for "relative standard deviation", a parameter for measuring drug content uniformity: the lower the RSD, the higher the uniformity):

Example No.	1	2	3	4	5	Comp.1	Comp.2
Particle	Lactose	Lactose	Lactose	Mannitol	Lactose	Mannitol	Lactose
Type	Granulated	Spray-dried	Spray-dried	Spray-dried	Granulated	Spray-dried	Agglomerat.
D ₉₀ (µm)	164	201	211	249	261	322	353
RSD (%)	0.7	1.4	1.5	1.0	1.3	3.8	3.0

The board agrees with the examining division that in order to make a conclusive comparison between the examples, only those having the same substance as carrier and particles of the same type may be compared, because it is well-known that factors such as particle shape, morphology, surface, density or roughness greatly affect the uniformity of a drug dispersed in a powder (see document (9), points 3.3 and 3.4; document (10), point 2.2.4 and conclusion; document (11), page 59, right column, paragraph 2; document (12), introduction). So, only a comparison of examples with the same carrier and particles of the same type allows a relationship to be established between particle size distribution (D₉₀) and drug content uniformity (RSD).

Following this principle, the analysis of the data in the table seems to confirm the trend noted by the

appellants that smaller carrier particles provide higher tablet uniformity. This is apparent from a comparison of the tablets containing spray-dried mannitol in example 4 and in comparative example 1, where a reduction of D_{90} from 322 μm to 249 μm results in an increase in drug uniformity with RSD falling from 3.8% to 1.0%. This trend can equally be observed within the D_{90} range defined in claim 1 when particles of the same type are compared. Thus, a comparison of the tablets with granulated lactose in examples 1 and 5 reveals that smaller particles effectively result in higher drug content uniformity (D_{90} = 164 μm , RSD= 0.7% vs. D_{90} = 261 μm , RSD= 1.3%). The same is true for the spray-dried lactose particles in examples 2 and 3 (D_{90} = 201 μm , RSD= 1.4% vs. D_{90} = 211 μm , RSD= 1.5%).

The board therefore agrees with the applicants that the examples plausibly show that, for the same type of particles, larger particles result in tablets with lower drug content uniformity. This trend however is plausibly shown not only for particles having a D_{90} of between 150 and 300 μm or above but also for particles having a D_{90} of less than 150 μm . This means that lactose or mannitol particles having a D_{90} of less than 150 μm can credibly be expected to provide tablets with a higher drug content uniformity than those according to claim 1.

This conclusion was not denied by the appellants at the oral proceedings before the board. However, the appellants argued that the demonstration of an improvement at the upper end of the claimed range was much more important than at the lower end, as the prior-art compositions would probably not contain mannitol or lactose particles with a D_{90} of below 150 μm . The board cannot agree with this reasoning. The

D₉₀ range in claim 1 is a selection from the non-specified particle sizes used in the prior art. Therefore, in order to demonstrate an improvement for the claimed range, it would be necessary to show the beneficial effect at both ends of the claimed range.

Hence, for this reason only, the board concurs with the examining division that the D₉₀ range disclosed in claim 1 does not provide tablets with improved content uniformity and that the problem to be solved has to be defined in a less ambitious way, as the provision of alternative prasugrel tablets.

2.5 The applicants did not provide additional arguments for the case that the problem had to be reformulated as an alternative. Hence, considering:

- i) that the tablets in claim 1 of the main request represent a selection from those disclosed in the closest prior art in that they have a defined D₉₀ range of lactose or mannitol particles;
- ii) that this selection is not associated with any technical effect; and
- iii) that the selected D₉₀ range encompasses values that are commonly used in the art, as may be inferred from the fact that all the particles tested in the application were commercially available at the filing date;

the board concludes that the subject-matter in claim 1 of the main request was an obvious selection for the skilled person. It therefore lacks an inventive step (Article 56 EPC).

3. *Inventive step - claim 1 of auxiliary request 1*

The limitations imposed in claim 1 of auxiliary request 1 do not amount to any additional difference from the closest state of the art. Formulation 4 in document (1) and the formulations in paragraphs [0046] and [0048] of document (2) disclose 200 mg prasugrel tablets containing 50 mg (25 wt.%) of a prasugrel salt, 124 mg (62 wt.%) lactose, 25 mg (12.5 wt.%) cellulose and 1 mg (0.5 wt.%) magnesium stearate. Considering that cellulose is a binder and magnesium stearate a lubricant (see application, paragraphs [0017] and [0016]), the only difference between the claimed tablets and the ones in documents (1) and (2) is, as in claim 1 of the main request, that their lactose particle size distribution is specified. Hence, for the reasons set out regarding the tablets in claim 1 of the main request, those in claim 1 of auxiliary request 1 lack an inventive step too (Article 56 EPC).

4. *Inventive step - claim 1 of auxiliary request 2*

According to the appellants, the limitations in auxiliary request 2 were intended to show more credibly that the particle size distribution defined in claim 1 resulted in tablets with improved content uniformity but were not associated with any additional effect.

Taking those limitations, in particular the restriction of component (A) to prasugrel hydrochloride, into consideration, the tablet in paragraph [0046] of document (2), which contains prasugrel hydrochloride as the active compound, may be considered the closest prior art.

The tablet in claim 1 differs from that closest prior art in that it contains slightly less active compound (1.3-20.0 wt.% vs. 25 wt.%) and slightly less binder (2.5 to 10.0 wt.% vs. 12.5 wt.%). As this difference does not produce any technical effect beyond the trend already recognised for the tablets in claim 1 of the main request, the problem to be solved has to be seen in the provision of further prasugrel hydrochloride tablets.

Having regard to the facts that the selection of $D_{90} = 150-300 \mu\text{m}$ was obvious to the skilled person (see point 2.5 above) and that a slight reduction in the amount of active compound and binder is merely a routine modification that the skilled person would make without expecting any associated effect to arise, the tablets in claim 1 of auxiliary request 2 do not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated