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**Datasheet for the decision  
of 11 March 2014**

**Case Number:** T 0771/13 - 3.3.01

**Application Number:** 04770646.0

**Publication Number:** 1618111

**IPC:** C07D495/00

**Language of the proceedings:** EN

**Title of invention:**

SALTS OF CLOPIDOGREL AND PROCESS FOR PREPARATION

**Applicant:**

CADILA HEALTHCARE LIMITED

**Headword:**

Clopidogrel besylate/CADILA

**Relevant legal provisions:**

EPC Art. 115, 84, 56

**Keyword:**

Observations by third parties - relevant (no)  
Clarity of the claims (yes) - characterisation of the product  
by two independent features  
Inventive step - non-obvious solution

**Decisions cited:**

**Catchword:**



**Beschwerdekammern  
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Case Number: T 0771/13 - 3.3.01

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.01**  
**of 11 March 2014**

**Appellant:**  
(Applicant)

CADILA HEALTHCARE LIMITED  
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**Decision under appeal:**

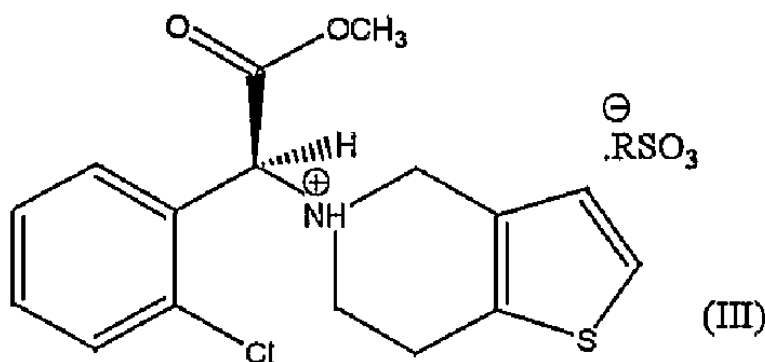
**Decision of the Examining Division of the  
European Patent Office posted on 5 November 2012  
refusing European patent application No.  
04770646.0 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman:** A. Lindner  
**Members:** C. M. Radke  
L. Bühler

### Summary of Facts and Submissions

- I. The patent applicant filed notice of appeal against the decision of the examining division posted on 5 November 2012 refusing European patent application No. 04 770 646.0.
- II. The application relates to clopidogrel besylate, i.e. the salt of clopidogrel with benzene sulfonic acid having the following general formula



where R means a phenyl group (see page 3 of the application).

- III. During the oral proceedings on 27 September 2012 before the examining division the applicant defended the patent application on the basis of the sets of claims of the main request and the first to fifth auxiliary requests.

Claim 1 of the main request and of the third auxiliary request read as follows:

"1. Unsolvated crystalline Clopidogrel besylate"

Claim 1 of the first and second auxiliary requests related to non-solvated and to solvent free crystalline clopidogrel besylate, respectively.

IV. The examining division decided in particular

- that the amended claims of the main request and of the first to third auxiliary requests contravene the requirements of Article 123(2) EPC due to the terms "unsolvated", "non-solvated" and "solvent free", respectively; and
- that the fourth and fifth auxiliary requests submitted during the oral proceedings were late-filed, did not prima facie overcome substantial objections and were thus not admitted into the proceedings.

V. The documents cited in the examination proceedings include the following:

- (D1) US-A-4 847 265
- (D4) WO-A-2004/072 084
- (D10) US-A-2005/0 203 122.

VI. The board issued a communication annexed to the summons to oral proceedings dated 17 December 2013 in which it *inter alia* gave reasons for its preliminary opinion that the claims characterising the crystalline clopidogrel besylate solely by reference to the X-ray diffraction spectrum of Figure 2 were unclear.

VII. Observations of a third party were filed by telefax on 7 March 2014 and included the argument that the subject-matter of the claims was not novel in view of the following document:

- (D11) DE-A-103 05 984.

VIII. During the oral proceedings before the board on 11 March 2014, the appellant withdrew all the previous sets of claims and presented a new set of claims as a basis of its main and sole request.

Claim 1 of the main request reads as follows:

"1. Crystalline Clopidogrel besylate having a powder X-ray diffraction pattern as depicted in Figure 2, having a melting point in between the range of 124 - 132 °C".

IX. The arguments of the appellant, as far as they are relevant for the present decision, may be summarised as follows:

*Clarity*

Whereas the line intensities of an XRD spectrum may vary depending on particle size, the line positions remain fixed. It was well known how to remove background intensities. As the spectra of the present application and that of document (D10) were taken on different machines, by different operators at different points in time, some variations are to be expected. Nevertheless, the peaks of both spectra match.

*Novelty*

Document (D4) only discloses the toluene and the dioxane solvates of crystalline clopidogrel besylate, which differ from the compound presently claimed.

*Inventive step*

Document (D1) is the closest prior art for assessing inventive step. The authors of (D1) were unable to prepare crystalline clopidogrel besylate. Initial attempts by the appellant yielded only a hygroscopic product as taught in document (D1). The person skilled in the art would not have attempted to make a salt which is reported to be hygroscopic. Moreover, the provision of a non-hygroscopic product over an earlier hygroscopic one has been considered to be inventive. The claimed compound has an improved shelf life as shown by submissions made during the prosecution. This is surprising and beneficial.

- X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed at the oral proceedings on 11 March 2014.
  
- XI. At the end of the oral proceedings the chairman announced the decision of the board.

**Reasons for the Decision**

- 1. The appeal is admissible.
  
- 2. Article 123(2) EPC

Present claim 1 is based on claim 7 and page 4, lines 16-17, of the application as originally filed. Claims 2 to 6 correspond to original claims 9 to 11, 26 and 30, respectively.

Hence, the board is satisfied that the amended claims do not contravene the requirements of Article 123(2) EPC.

3. Observations by a third party (Article 115 EPC)

These observations were received by the EPO via telefax on Friday, 7 March 2014 at 4.43 pm. The oral proceedings before the board took place on Tuesday, 11 March 2014. The novelty objection was based on document (D11), a German patent application which does not form part of

- the state of the art under Article 54(2) EPC as it was published after the date of filing of the present application; nor does it form part of
- the state of the art under Article 54(3) EPC since it is not considered to be a European patent application as it was not filed under the provisions of Rule 35 EPC.

So, this novelty objection was not based on state of the art under the EPC. Moreover, the remaining documents and objections were not *prima facie* more relevant than those raised previously.

Hence, it was evident that these observations could not have any influence on the outcome of the present decision. Consequently there was no need to decide whether or not to admit these late-filed observations (see Article 13(3) of the Rules of Procedure of the Boards of Appeal, OJ EPO Supplementary publication 1/2004, 44).

4. Clarity of the claims (Article 84 EPC)

4.1 The board considered that the reference to the X-ray diffraction spectrum as depicted in Figure 2 left room for interpretation as

- the relative line intensities depend on the particle size;
- the peaks cannot always be distinguished from noise due to background scattering; and
- the numerical values of the angle  $2\theta$  the peaks obtained from Figure 2 may vary to a certain degree.

The latter is primarily due to the fact that numerical values obtained from Figure 2 are bound to be less accurate than those directly obtained from the processed film.

The board is, however, well aware that X-ray diffraction is a valuable tool for distinguishing different crystalline forms.

4.2 Another feature which is independent of X-ray diffraction and by which solid pure compounds (except pairs of enantiomers of a chiral molecule) may be distinguished is the melting point. In the present case, crystalline forms of the besylate salt of clopidogrel are to be distinguished, i.e. the benzenesulfonates of the S(+)-enantiomer (i.e. of the same enantiomer) of methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate (see formula (III) depicted under point II above). Hence, the melting point appears to be characteristic for such a form. This is confirmed by the fact that the range of from 124-132°C indicated in present claim 1 is much higher than the ranges indicated for the melting points of the amorphous mesylate, besylate and tosylate salts



of clopidogrel (see page 4, lines 11-19, of the present application) and of the crystalline solvates of clopidogrel besylate with toluene or dioxane (see document (D4), example 1 (where a range of 87-90°C is given for the melting point of the toluene solvate) and example 2 (where a range of 93-95°C is given for the dioxane solvate)).

- 4.3 It may therefore be concluded that the characterisation of the compound of present claim 1 **both** by the X-ray diffraction pattern of Figure 2 **and** by the range of from 124-132°C for the melting point allows the person skilled in the art to distinguish clearly one form of crystalline clopidogrel besylate from another.

Therefore, claim 1 is clear. The board ascertained that the remaining claims are also clear.

## 5. Novelty

Novelty was not under dispute. The only prior art disclosing crystalline clopidogrel besylate is document (D4), which describes the preparation of the respective toluene and dioxane solvates. The present claims relate to a certain crystalline clopidogrel besylate (claims 1 and 2), processes for making it (claims 3 and 4), a pharmaceutical composition containing the same (claim 5) and to its second medical use (claim 6). The subject-matter of these claims differs from that disclosed in document (D4) *inter alia* in that the melting point of the present product is considerably higher (see point 4.2 above).

Hence, the subject-matter of the present claims is novel.

6. Inventive step (Article 56 EPC)

6.1 Document (D4) was published on 26 August 2004, i.e. after the date of filing of the present application. Therefore, it only forms part of the state of the art under Article 54(3) EPC and is not to be considered when assessing inventive step (see Article 56 EPC, second sentence).

6.2 Closest prior art

The board agrees with the appellant that document (D1) is to be considered the closest prior art for assessing inventive step.

This document claims clopidogrel and its pharmaceutically acceptable salts (see claim 1 and formula (I) in column 1). Such salts include the hydrochloride, hydrogensulfate, hydrobromide and the taurocholate (see claims 2 to 5). Examples 1 and 2 disclose the preparation of all these salts in crystalline form (see e.g. example 1, particularly column 6, lines 17, 45 and 60; column 7, lines 6 and 31).

The only reference to the benzenesulfonic acid salt (i.e. the besylate) is found in column 1, lines 45-62, of this document, which read as follows:

"The compound (I<sub>d</sub>) is an oil whereas its hydrochloride exists as a white powder. The oily products are usually difficult to purify and it is preferable to use for the preparation of pharmaceutical compositions crystalline products which can usually be purified by recrystallization.

However, it has been observed in the present case that some of the salts of compound (Id) usually precipitate in an **amorphous form and/or** that they are **hygroscopic**, a property which makes them difficult to handle on an industrial scale. Thus, the salts of carboxylic acid and sulfonic acids classically used in pharmacy have been prepared, acids such as acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methane-sulfonic, ethanesulfonic, **benzenesulfonic** and laurylsulfonic acids as well as the salts of dobesilic acid (m.p.= 70°C.) and para-toluenesulfonic acid (m.p.=51°C.), the purification of which proved to be difficult" (emphasis added by the board).

In short, these paragraphs imply that the clopidogrel besylate was among the salts obtained which proved to be amorphous and/or hygroscopic. Hence, document (D1) does not directly disclose crystalline clopidogrel besylate.

### 6.3 Problem and solution

The present application considers it as the object of the claimed invention "to prepare new pharmaceutically acceptable salts of Clopidogrel", and, particularly, to provide these "salts in pure, easy to handle, free flowing and stable form" (see page 2, lines 25-26 and 32-33).

According to page 15, lines 6-8, of the letter dated 11 February 2014, Annex G to this letter demonstrates the long-term stability of the product presently claimed. This annex shows that said product

- shows no signs of deterioration after storage at 25°C and 60% relative humidity for one year and after storage at 40°C and 75% relative humidity

- for six months (see the information on the "Assay of ... (By HPLC)" in the tables); and
- does not take up any considerable amount of water during said storage, i.e. that it is not hygroscopic (see the information on the "Water content" in the tables).

The crystalline nature of the product permits its purification by recrystallisation. The fact that it is not hygroscopic contributes to its easy handling and its free flow.

For these reasons, the subject-matter presently claimed solves the problem of providing new pharmaceutically acceptable salts of clopidogrel which are stable, free flowing, easy to handle and to purify.

#### 6.4 Obviousness of the solution

As mentioned under point 6.2 above, document (D1) discloses that clopidogrel besylate was among the salts obtained which proved to be amorphous and/or hygroscopic.

Therefore, document (D1) discourages the person skilled in the art from preparing this salt when solving the problem mentioned above. This holds the more as column 1, lines 45-62, of this document refers only to salts of carboxylic and sulfonic acids, so that the skilled person knew alternative pharmaceutically acceptable acids, such as nitric, phosphoric and thiocyanic acids.

Hence, the subject-matter of the present main request was not obvious to the person skilled in the art.

For these reasons, said subject-matter is based on an inventive step.

7. The board ascertained that the present claims also meet the other requirements of the EPC.

## Order

### For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent with the following claims and a description to be adapted:  
Claim(s):  
Nos. 1 to 6 of the main request received during the oral proceedings on 11 March 2014.

The Registrar:

The Chairman:



G. Nachtigall

A. Lindner

Decision electronically authenticated