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Datasheet for the decision of 18 June 2014

Case Number: T 0643/12 - 3.3.01

Application Number: 04807580.8

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Language of the proceedings: EN

Title of invention:

CRYSTAL OF SALT OF 4-(3-CHLORO-4-(CYCLOPROPYLAMINOCARBONYL)AMINO-PHENOXY)-7-METHOXY-6-QUINOLINECARBOXAMIDE OR OF SOLVATE THEREOF AND PROCESSES FOR PRODUCING THESE

Applicant:

Eisai R&D Management Co., Ltd.

Headword:

Lenvatinib mesylate polymorphs/EISAI

Relevant legal provisions:

EPC Art. 123(2), 84, 54, 56
EPC R. 43(6)

Keyword:

Main request: inventive step (yes) - unexpected balance of properties

Decisions cited:

T 0777/08

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Case Number: T 0643/12 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 18 June 2014

Appellant: (Applicant)	Eisai R&D Management Co., Ltd. 6-10, Koishikawa 4-chome Bunkyo-ku Tokyo 112-8088 (JP)
Representative:	C. Stein-Dräger, HOFFMANN EITLE Patent- und Rechtsanwälte Arabellastrasse 4 81925 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 25 October 2011 refusing European patent application No. 04807580.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	L. Seymour
	L. Bühler

Summary of Facts and Submissions

I. The present appeal lies from the decision of the examining division refusing the European patent application No. 04 807 580.8, with filing date of 22 December 2004 and claiming priority of 25 December 2003 from the Japanese patent application No. 2003430939.

II. The following documents, cited during the examination and appeal proceedings, are referred to below:

(1) EP-A-1 797 881

(2) EP-A-1 415 987

(2a) WO 02/32872

(4) R J Bastin et al., Org. Process Res. Dev., 2000, 4(5), 427-435

(5) P L Gould, Int. J. Pharm., 1986, 33, 201-217

(6) S M Berge et al., J. Pharm. Sci., 1977, 66(1), 1-19

(8) R T Forbes et al., Int. J. Pharm., 1995, 126, 199-208

(13) Japanese Pharmacopoeia 14th Edition in English translation, p. 44, 45, 112, 113 (retrieved from http://jpdb.nihs.go.jp/jp14e/contents.html)

(14) Handbook of the Japanese Pharmacopoeia, 14th edition, B—6l4 to 619, English translation attached to appellant's letter

dated 13 June 2014

III. The decision under appeal was based on the main and sole request filed with letter dated 22 September 2011.

The examining division considered that the subject-matter claimed lacked an inventive step. The closest prior art was identified as being document (2), and the problem to be solved defined as lying in improving the solubility and bioavailability of lenvatinib (4-(3-chloro-4-(cyclopropylaminocarbonyl)-aminophenoxy)-7-methoxy-6-quinolinecarboxamide). With reference to the data present in the application and the additional data filed with letter dated 30 June 2011, the examining division acknowledged that the solution of forming the methanesulfonate (mesylate) salt solved said problem. However, this solution was found to be obvious in the light of the general knowledge as disclosed in document (6). Reference was made in this context to decision T 777/08.

IV. With the statement of grounds of appeal, the appellant (applicant) submitted a main request and an auxiliary request.

V. In a communication by the board dated 18 March 2014, sent as an annex to the summons for oral proceedings, the issue of inventive step was discussed.

VI. With letter dated 16 May 2014, the appellant filed replacement main and auxiliary requests, and provided additional arguments in favour of inventive step.

VII. In a further communication dated 30 May 2014, the board stated that it was now minded to acknowledge an

inventive step for the subject-matter of the main request.

VIII. With letter dated 16 June 2014, the appellant filed a new main request to address remaining formal objections raised by the board.

Claim 1 of this request reads as follows:

"1. Crystalline form A and C of 4-(3—chloro—4—(cyclopropylaminocarbonyl)aminophenoxy)-7—methoxy-6-quinolinecarboxamide methanesulfonate, wherein crystalline form A has diffraction peaks at diffraction angles (2θ ± 0.2°) of 9.65° and 18.37° and wherein crystalline form C has diffraction peaks at diffraction angles (2θ ± 0.2°) of 14.20° and 17.59° in a powder X—ray diffraction measured according to "X-Ray Powder Diffration Method" described in Japanese Pharmacopoeia, 14th Edition, General Test utilizing the equipment and the condition as described in the description."

IX. By communication dated 16 June 2014, oral proceedings appointed for 18 June 2014 were cancelled.

X. The appellant (applicant) requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with letter dated 16 June 2014 or, alternatively, on the basis of the auxiliary request filed with letter of 16 May 2014.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Amendements (Article 123(2) EPC)*

The subject-matter of the main request meets the requirements of Article 123(2) EPC.

In particular, claim 1 is based on claims 4, 10 and 15 as originally filed, in conjunction with page 49, lines 2 to 18. It is noted in this context that, on page 49, line 5, reference is erroneously made in brackets to the page numbers "B-614 to 619" (see also page 53, line 29), which relates to the "Handbook of the Japanese Pharmacopoeia" rather than the "Japanese Pharmacopoeia". However, since the relevant passages of both these texts are identical in wording (cf. document (13), section 69; and document (14), section 57), the omission of said page numbers in claim 1 is not considered to contravene Article 123(2) EPC.

3. *Article 84 EPC*

In the present claims, the level of detail provided with respect to the methods of measurement, when necessary with additional reference to the description (see below), is such as to allow clear and reliable determination of the parameters defined.

In claims 1, 2, 4 and 9, reference is made to the description with respect to the equipment and conditions to be used in determining the corresponding parameters. This is considered to represent an allowable exception in accordance with Rule 43(6) EPC, since the specific passages of the description referred to are readily identifiable (see page 49, lines 2 to 18 and page 63, lines 1 to 11), and the conciseness and readability of the claims in question would suffer from a complete recitation of said passages therein.

In addition, in claims 1, 3, 5 and 9, reference is made to test methods described in the "Japanese Pharmacopoeia, 14th Edition". This is not considered to be objectionable under Article 84 EPC since the cross-referenced document is an official text that is readily retrievable in English translation, and the corresponding passages relating to the test methods cited are clearly identifiable therein (cf. document (13)).

Consequently, the claims of the main request are considered to fulfil the requirements of Article 84 EPC.

4. *Novelty (Articles 52(1), 54 EPC)*

In the decision under appeal, no novelty objections were raised, and the board sees no reason to differ.

The only cited document to disclose specific polymorphs of lenvatinib mesylate is document (1) (see paragraphs [0024] and [0025]). However, its priority date of 17 September 2004 is later than the present priority date (cf. above point I), which is validly claimed for the relevant subject-matter of the main request.

Document (1) does not therefore constitute prior art in the sense of Article 54 EPC.

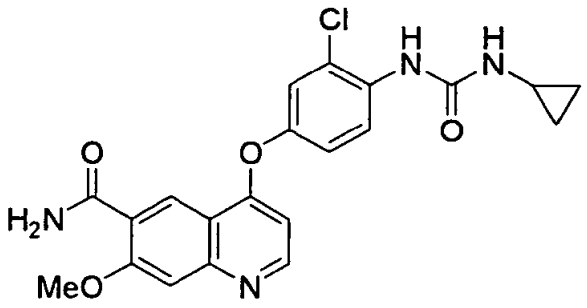
The subject-matter of the main request is therefore considered to be novel.

5. *Inventive step (Articles 52(1), 56 EPC)*

5.1 The subject-matter of claim 1 relates to crystalline forms A and C of lenvatinib mesylate. According to page 31, lines 10 to 19 of the present description, these are useful as angiogenesis inhibitors, anti-tumour agents, cancer metastasis inhibitors, and as therapeutic agents for treating a range of diseases such as angioma, retinal neovascularisation, diabetic retinopathy, an inflammatory disease, or atherosclerosis.

5.2 Document (2a) represents the closest state of the art (see also present application, paragraphs [0002] and [0003]). Since this document is written in Japanese, reference will be made below to its family member document (2), which, although published after the priority date of the application in suit, can be considered to represent a correct translation of document (2a) (cf. decision under appeal, paragraph bridging pages 7 and 8; statement of grounds of appeal, page 3, first sentence).

In paragraph [0244], document (2) discloses a similar range of activities as the present application. In Example 368 (page 193), lenvatinib is prepared in the form of white crystals. The structure of this compound is as follows (cf. page 338, line 35, middle):



5.3 The problem to be solved in the light of document (2) may be defined as lying in the provision of lenvatinib in a form having an improved dissolution rate and bioavailability, low hygroscopicity, and good stability.

The solution proposed in claim 1 relates to the mesylate salt of lenvatinib in crystalline forms A and C, defined in terms of specific X-ray powder diffraction peaks.

Based on the experimental results reported in Test Examples 1 to 3 of the present application (page 44, line 22 to page 52, line 16) and the additional bioavailability data provided with letter dated 30 June 2011 (page 4), the board is satisfied that the problem posed has been solved. It is noted in this context, that an error appears to have occurred in Test Example 3, since Tables 4 and 5 are identical in content and both refer to Form C (pages 49, 50). However, in view of the statement on page 50, lines 9 to 13, the board sees no reason to doubt that the Form A, like Form C, exhibits low hygroscopicity.

5.4 It remains to be investigated whether the proposed solution is obvious to the skilled person in the light of the prior art.

5.4.1 The skilled person starting from lenvatinib as disclosed in document (2) (see above point 5.2) would be aware of its physicochemical properties, and specifically that it is a weak base, by virtue of the presence of the quinoline moiety, with poor aqueous solubility. Moreover, the skilled person would be familiar with the standard literature relating to pharmaceutical salts.

For example, document (4), which is an article entitled "Salt Selection and Optimisation for Pharmaceutical New Chemical Entities", discloses that salt formation can be employed to modify a number of properties, including those listed above in point 5.3 (page 427, Abstract).

It is further stated on page 428, penultimate paragraph:

"The vast majority of salts are developed to enhance the aqueous solubility of drug substances. For weakly basic drug substances, salts of an inorganic acid (e.g., hydrochloride, sulphate, or phosphate), a sulphonic acid (mesylate or isethionate), a carboxylic acid (acetate, maleate or fumarate), a hydroxyacid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered."

Similar teachings are to be found in documents (5) and (6), which are general articles entitled "Salt selection for basic drugs" and "Pharmaceutical Salts", respectively (cf. document (5), Summary and Table 1; document (6), page 1, left-hand column, and Table I).

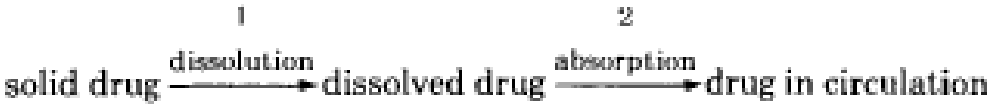
More specifically, document (6) teaches that it is generally possible to achieve improved dissolution rates and bioavailability by formation of salts,

particularly with poorly soluble drugs. Thus, the section entitled "Dissolution Rate", bridging pages 5 and 6 of document (6), reads as follows:

"The dissolution rate of a pharmaceutical agent is of major importance to the formulator. In many cases, particularly with poorly soluble drugs, this characteristic best reflects the bioavailability of the compound. As a rule, a pharmaceutical salt exhibits a higher dissolution rate than the corresponding conjugate acid or base at an equal pH, even though they may have the same equilibrium solubility."

Similarly, in the section entitled "Bioavailability", the following is disclosed (page 10):

"Most drugs prescribed in the United States are administered in solid and polyphasic dosage forms. Consequently, dissolution of the drug must precede the absorption process. The simplest model that adequately describes this process is shown in Scheme II.



Scheme II

Since the dissolution rate is generally slow for drugs with poor solubility, Step 1 is frequently rate limiting in the overall absorption process. As a result, the onset, intensity, duration of pharmacological activity, and, hence, bioavailability are affected by changes in dissolution rate. As discussed previously, administering a salt of the parent drug often proves to be an effective means of altering dissolution rate and absorption."

This teaching is confirmed in document (5) (see page 208, right-hand column, first complete paragraph).

The appellant pointed to document (8) in this context, as providing an example in which formation of a tosylate salt led to a decrease in dissolution rate under specific conditions (cf. document (8), page 207, Table 3, last two lines). However, a single result of this type cannot detract from the validity of the general trends as outlined above. It is noted in this context that, for all other entries of Table 3, an increase in dissolution rate was observed on salt formation.

The board therefore concludes, in agreement with the view expressed in the decision under appeal (cf. above point III), that salt formation with acids of the type suggested in documents (4) to (6), including methanesulfonic acid, would be one of the avenues that the skilled person would consider in the expectation of increasing the dissolution rate and bioavailability of lenvatinib.

5.4.2 However, salt formation is not the only feature reflected in claim 1; indeed, further restrictions are present defining specific crystalline forms of the mesylate salt (cf. above point VIII). These polymorphs have been found to exhibit low hygroscopicity, and to be stable under various conditions of humidity, temperature and light (see Test Example 3; cf. also above point 5.3). The importance of such properties in determining the viability of a pharmaceutical salt emerges clearly from documents (5) and (6) (cf. document (5), page 203, left-hand column, first complete paragraph, second sentence; document (6), page 9, left-hand column, penultimate paragraph).

Therefore, in order to fully assess the issue of inventive step, it must be established whether there was any suggestion in the prior art that would have led the skilled person to expect that the subject-matter claimed would provide the present combination of favourable properties, not only in terms of solubility and bioavailability, but also hygroscopicity and stability, as reflected in the problem defined above in point 5.3.

In document (5), it is cautioned that "the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice" (page 201, left-hand column). Only first-line suggestions of a general nature are provided in this respect, as summarised in Figure 5 (page 211; see also page 212, first complete paragraph). It can be seen from the flow charts depicted in Figure 5 that improvement in one desired property may be to the detriment of another, as further exemplified in the following excerpt from document (5) (page 210, first complete paragraph of the right-hand column):

"Although the xilobam example above serves to demonstrate that one has to consider the hydrophobicity of the conjugate anion to control salt stability, it is clear that this property is pivotal on two others; salt hygroscopicity and wettability. Thus, once again, a balance of salt properties is required so that hygroscopicity is not reduced at the gross expense of salt wettability leading ultimately to dissolution rate and bioavailability problems".

The difficulties in providing clear guidance with respect to salt selection are confirmed in the further

prior art cited. For example, it is emphasised in document (6) that "Choosing the appropriate salt ... can be a very difficult task, since each salt imparts unique properties to the parent compound" (page 1, left-hand column, last sentence).

Moreover, having identified a promising salt form, the skilled person is presented with further degrees of freedom in manipulating the properties thereof, for example, by the potential for polymorph formation (see e.g. document (5), last sentence of paragraph bridging pages 210 and 211). Again, no teaching is provided in the prior art as to how this property may be exploited in a targeted manner in order to achieve the desired combination of properties.

It is therefore concluded that the skilled person would not derive any pointer from the prior art to the effect that the solution to the present problem was to be sought in particular polymorphs of the mesylate salt of lenvatinib.

5.4.3 The facts of the present case differ from those underlying decision T 777/08 (OJ EPO 2011, 633) discussed in the decision under appeal (point 3.7). In that case, the starting point was the amorphous form of atorvastatin, and it was found that the skilled person would have a clear expectation that a crystalline form thereof would provide a solution to the problem of providing a product having improved filterability and drying characteristics; the specific polymorph claimed was found to be an arbitrary selection from a group of equally suitable candidates for solving the problem posed (see point 5 of reasons). In contrast, in the present case, as explained above in point 5.4.2, the the specific polymorphs of the mesylate salt claimed

would not have been expected to deliver the desired combination of properties. Moreover, the skilled person would not have had a reasonable expectation that any arbitrary crystalline salt form of lenvatinib would be equally suitable in this respect. This lack of equivalence is illustrated in the application in suit, wherein the mesylate salt designated as Form I (acetic acid solvate) is demonstrated to be unstable under certain conditions where Forms A and C are stable (cf. Tables 8 to 10, entries d-2 and e-2).

5.5 In view of the above considerations, the board concludes that the subject-matter of claim 1 of the main request involves an inventive step. The same applies to dependent claims 2 to 5, and the remaining claims 6 to 13 relating to processes of preparation, pharmaceutical compositions and uses thereof.

Accordingly, the subject-matter of the main request meets the requirements of Articles 52(1) and 56 EPC.

6. Since the main request is considered to be allowable, it is not necessary to comment on the auxiliary request.

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 on the basis of claims 1 to 13 of the main request as filed with letter of 16 June 2014 and a description to be adapted thereto.

The Registrar: The Chairman:

G. Nachtigall A. Lindner

Decision electronically authenticated