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Datasheet for the decision of 2 July 2009

Case Number: T 1618/06 - 3.3.01

Application Number: 01909568.6

Publication Number: 1169314

IPC: C07D 307/87

Language of the proceedings: EN

Title of invention:
Crystalline base of citalopram

Patentee:
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Egis Gyógyszergyár NYRT.
Merck dura GmbH
Niche Generics Limited
Merck N. V.

Headword:
Purification of citalopram/LUNDBECK

Relevant legal provisions:
EPC Art. 87(1), 100(a)
EPC R. 115(2)

Keyword:
"Priority (valid) - feature disclosed in the section describing the prior art is referred to in the remaining part of the description"
"Novelty (yes)"
"Inventive step (yes) - non obvious solution"

Decisions cited:
-

Catchword:
-

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Case Number: T 1618/06 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 2 July 2009

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 15 September 2006 revoking European patent No. 1169314 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: P. Ranguis
Members: C. M. Radke
C.-P. Brandt

Summary of Facts and Submissions

I. The patentee appealed the decision of the opposition division to revoke European patent no. 1 169 314.

II. The oppositions were based on grounds under Article 100 (a) (alleged lack of novelty and inventive step), (b) and (c) EPC.

III. The following documents were *inter alia* cited during opposition proceedings:

(D1) DE-A-26 57 013
(D3) EP-A-0 347 066
(D5) WO-A-00 11 926
(D6) WO-A-00 13 648
(D9) R. B. Bates and J. P. Schaefer, Research Techniques in Organic Chemistry, Prentice-Hall Inc, Englecliffs, N.J./US, 1971, 50-52
(D12) PCT/DK00/00 183 filed on 13 April 2000
(D13) WO-A-01 02 383
(D18) WO-A-98 19 512
(D19) WO-A-98 19 511
(D20) WO-A-98 19 513
(D29) Communication of WIPO dated 13 September 2001 concerning PCT/EP00/06 426
(D30) Declaration of Trevor Laird dated 06 March 2002, 16 pages including enclosures
(D31) Declaration of Hans Petersen dated 06 May 2002, 14 pages including enclosures

IV. The opposition division decided

(a) that the intervention of the assumed infringer (Merck N.V.) was admissible;

(b) that the insertion of the expression "from a solvent, and thereafter separated from the solvent" was admissible under Article 123(2) EPC;

(c) that the non-optional features of claim 1 of the main request enjoyed the priority of 13 April 2000 whereas the priorities were not valid for claim 3 of the main request and claim 1 of the auxiliary request;

(d) that the subject-matter of claim 3 of the main request was not novel in view of document (D13), whereas documents (D1), (D3), (D5) and (D6) did not deprive the subject-matter claimed of novelty; the subject-matter of the claims of the auxiliary request was, however, novel, but not inventive in view of the closest prior art (D5) if combined with the disclosure of (D13).

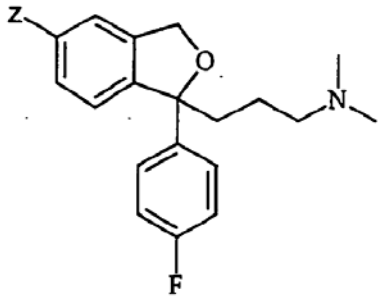
V. The decision under appeal was based on claims 1 to 10 as granted (main request) and claims 1 to 7 of the auxiliary request submitted during the oral proceedings of 19 July 2006.

(a) Independent claims 1 and 3 of the main request read as follows:

"1. A process for the manufacture of a salt of citalopram **characterised in that** the base of citalopram is set free and precipitated in crystalline form from a solvent, and thereafter separated from the solvent and optionally re-

crystallised one or more times, and then transferred into a salt thereof."

"3. A process for the manufacture of citalopram base or a salt of citalopram **characterised in that** one or more impurities of the formula

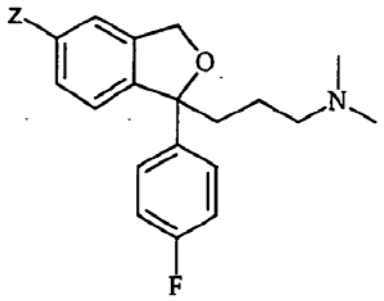


(II)

wherein Z is halogen, $-O-SO_2(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof."

(b) Claim 1 of the auxiliary request reads as follows:

"1. A process for the manufacture of citalopram base or a salt of citalopram **characterised in that** one or more impurities of the formula



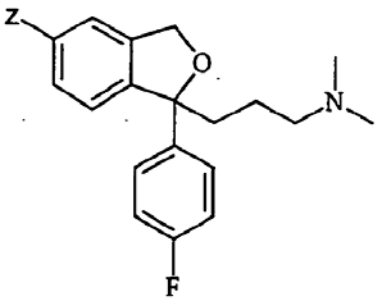
(II)

wherein Z is halogen, in particular bromide or chloride, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof."

VI. The claims on which the present decision is based are claims 1 to 7 of the amended Main Request filed during the oral proceedings before the Board on 02 July 2009.

Claim 1 of the amended Main Request (hereinafter called Main Request) reads as follows:

"1. A process for the manufacture of a salt of citalopram **characterised in that** one or more impurities of the formula



(II)

wherein Z is halogen, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by

precipitating citalopram base in crystalline form, and transferring said base into a salt thereof."

VII. The following document was additionally cited during the appeal proceedings:

(D38) DE-U-200 07 303.

VIII. The relevant arguments of the Appellant raised during the appeal proceedings may be summarised as follows:

Claim 1 enjoyed the priority of 13 April 2000 as its subject-matter was disclosed in claims 5 and 6 and on page 2 of the priority document (D12).

As to novelty, it argued

- that document (D5) did not disclose to remove the impurities by precipitating citalopram in crystalline form, and
- that document (D13) did not form part of the prior art as the present claims enjoyed the priority of document (D12).

As to inventive step, it considered the problem to be solved in view of document (D5) to prepare citalopram in purer form. This problem was solved as was evident from the experimental evidence provided in documents (D30) and (D31). There were several other methods of purification known in the prior art and there was no indication that the precipitation in crystalline form would purify citalopram so effectively. The person skilled in the art would not have crystallised citalopram base as this was an intermediate in the multistep process yielding its salt; crystallisation

was normally carried out discontinuously, whereas a multistep process was preferably carried out continuously.

IX. The Respondents argued that claim 1 did not enjoy the priority of document (D12) because the impurities mentioned in this claim were only disclosed in document (D12) with respect to the prior art cited therein.

They considered claim 1 not to be novel in view of document (D13) or (D5). As to inventive step, they argued that it was clear that the "improved crystalline product" referred to in document (D5) was the base. It was obvious to crystallise the base as the different polarity of the base and of its salts permitted the separation of different impurities using different solvents. Therefore, they deemed the subject-matter of the claims of the Main Request not to involve an inventive step.

X. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the Main Request filed during the oral proceedings before the Board on 02 July 2009.

The Respondents requested that the appeal be dismissed.

XI. The Respondents Merck dura GmbH, Niche Generics Limited and Merck N.V. had been duly summoned to the oral proceedings before the Board but were absent as indicated in their letters dated 02 June, 24 February and 15 May 2009, respectively. The proceedings were thus continued in the absence of these Respondents in accordance with Rule 115(2) EPC.

XII. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123 EPC*

Claim 1 is based on claims 3 and 5 as originally filed. Claims 2-7 are based on original claims 4 and 6-10.

The amendments in the claims resulted in the deletion of claims 1, 2 and 5 as granted and in the limitation in the scope of claims 3 and 8 as granted.

The amended claims thus meet the requirements of Article 123 (2) and (3) EPC.

3. *Priority (Article 87(1) EPC)*

3.1 Claim 1

It was under dispute whether or not the following feature of present claim 1 enjoyed the priority of document (D12): The removal of the impurity of formula (II).

Hence it has to be assessed whether or not document (D12) teaches the person skilled in the art

– to remove impurities from a crude mixture or a

crude salt of citalopram, and, in the affirmative,

– whether or not these impurities comprise those of formula (II) as defined in present claim 1.

3.1.1 The part of document (D12) disclosing the invention claimed therein starts with the fourth paragraph on page 2 ("It has now been found that ..."). The second sentence of this paragraph states that the invention provides " ... a very good and efficient purification of citalopram ...". The starting material used in this purification process is crude salt or crude mixture of citalopram (see (D12), the fourth paragraph on page 3). Hence, document (D12) discloses a process removing impurities from a crude mixture or a crude salt of citalopram.

3.1.2 It remains to be determined whether or not document (D12) discloses directly and unambiguously that the impurities to be removed comprise those of formula (II) as defined in present claim 1. The process disclosed in document (D12) is to purify citalopram or its salt. This means that the impurities are present in the crude starting material. This starting material " ... may be obtained directly from the synthesis of the compound **according to any of the above mentioned processes ... "** (see page 3, fifth paragraph, lines 8-11; emphasis added by the Board). The "above mentioned processes" are those summarised in the first and second paragraphs on page 2, including the "Exchange of 5-halogen with cyano ... " (see page 2, lines 1-2). The impurities present in the reaction mixtures obtained in these processes comprise "... the intermediates mentioned above ..." (see the third paragraph on page 2), namely the 5-halogen compound as far as the process comprising

the exchange of 5-halogen by a cyano group is concerned. Consequently, the chemical formula of this impurity differs from the formula of citalopram as depicted on page 1 of document (D12) only in that the cyano group in the 5-position is replaced by a halogen atom; that means that it is identical with formula (II) depicted in present claim 1.

Hence, document (D12) discloses a process by which impurities of formula (II) as defined in present claim 1 are removed from a crude mixture or a crude salt of citalopram.

It is not relevant that part of this disclosure is based on the description of the prior art, as document (D12) directly refers to said prior art in the paragraphs setting out the invention claimed therein (see the first paragraph under point IX above).

3.1.3 The remaining features of claim 1 of the Main Request are disclosed in claim 5 of document (D12).

3.2 The priority of the additional features of claims 2 to 7 was not under dispute. Their subject-matter is disclosed in the priority document (D12) as follows:

Claim 2:	(D12), page 2, lines 1-2;
claims 3 and 4:	(D12), page 3, lines 25-28;
claim 5:	(D12), claim 6 and the bottom paragraph on page 3;
claim 6:	(D12), claim 7;
claim 7:	(D12), claim 8.

3.3 Hence, the priority of 13 April 2000 based on document (D12) is valid for the present claims. This has the effect that

- document (D13) which has a filing date of 06 July 2000 and the priority of which has been withdrawn before publication (see document (D29)), and
- document (D38), a German utility model published on 31 August 2000

do not form part of the state of the art for the patent in suit.

4. *Novelty*

4.1 *Document (D3)*

The Respondents did not consider the subject-matter of the claims of the Main Request to lack novelty in view of document (D3). These claims are now restricted to a process which involves the removal of impurities of the formula (II) of claim 1 (where Z means a halogen atom) from a crude mixture or crude salt of citalopram. Document (D3) does not disclose a process involving a starting material or intermediate of said formula (II) (see the reaction schemes on pages 4 and 5 of document (D3)). Therefore, the reaction mixture obtained in the process disclosed in document (D3) does not contain compounds of formula (II) as defined in present claim 1, with the effect that such compounds cannot be removed from the reaction mixture as required in the present claims.

4.2 *Document (D5)*

4.2.1 This document discloses a method for preparing citalopram by reacting the 5-chloro or 5-bromo derivative with a cyanide source (see claim 1). In the only example, the reaction mixture was diluted with diethyl ether, filtered, the filtrate was washed, dried and concentrated under reduced pressure. The residue was dissolved in acetone, and oxalic acid was added to produce citalopram oxalate. The document mentions that "Finally, this process gives an improved crystalline product enabling easy conversion to desired salts." (page 4, lines 13-14).

4.2.2 The Respondents argued that all the process features of present claim 1 were disclosed in document (D5), in particular in the only example if combined with the general disclosure on page 4 that the product is crystalline (see point 4.2.1 above).

4.2.3 Present claim 1 requires that one or more impurities of formula (II) are removed from the crude citalopram or its salt by precipitating the base in crystalline form and transferring the base into a salt.

This means that impurities of formula (II) are removed during these process steps. In the example of document (D5) the only substance removed from the reaction mixture from the moment where the base is precipitated to the one where the salt is formed is the solvent (diethyl ether) which is distilled off under reduced pressure. There is no disclosure in this example nor in document (D5) in general, that impurities of formula

(II) as defined in present claim 1 could be removed during these process steps.

4.2.4 Hence, document (D5) does not disclose all the features of present claim 1.

4.3 Therefore, the subject-matter of present claim 1 is novel. The same applies to the subject-matter of dependent claims 2-7 which relate to improved embodiments of the process of claim 1.

5. *Inventive step*

5.1 *The closest prior art*

The parties considered document (D5) to represent the closest prior art. The disclosure of this document has the most relevant features in common with the subject-matter of present claim 1 (see points VI and 4.2.1 above). Furthermore it shares the objective with the patent in suit to provide a process yielding a pure salt of citalopram (see paragraph [0008] of the patent in suit and document (D5), page 3, lines 10-14, and page 5, lines 20-21). Therefore, document (D5) is indeed the closest prior art.

5.2 *The problem to be solved*

The patent in suit cites document (D5) (see page 2, line 37). The problem addressed in the patent in suit is to provide "a very good and efficient purification of citalopram" (see paragraph [0008]). Document (D31) shows that the crystallisation of citalopram base yields crystals containing considerably less impurities

of formula (II) as defined in present claim 1 as compared to the crystallisation of citalopram hydrobromide or oxalate (see (D31), the table on page 4). Hence, the claimed invention does indeed solve the problem to provide a process yielding citalopram salt in a purer form.

5.3 *Obviousness of the solution as claimed*

According to document (D5), "citalopram may be obtained in a high yield as a very pure product by a new catalytic process", namely by using a nickel catalyst. (see page 3, lines 10-13 and 23). Hence, this document gives the impression that the catalyst - and not the crystallisation mentioned on page 4, lines 13-14 - is the cause of the increased purity of the product.

The person skilled in the art trying to modify the process disclosed in document (D5) in such a way that a purer citalopram salt is obtained has several options (see, e.g., the ones used in the tests of document (D30)).

The Respondents referred to document (D9) to show that crystallisation was the most obvious way to solve this problem (see (D9), page 50, lines 1-4 under the heading "2.2 CRYSTALLIZATION"). Document (D5) does in fact suggest purification by means of crystallisation and recrystallisation of the oxalate **salt of citalopram** (see the only example, in particular its last sentence).

In contrast thereto, present claim 1 requires purification by crystallisation of **citalopram base.**

In many of the processes of the prior art, citalopram base is obtained as an oil (see document (D1), page 22, lines 8-12; (D18), page 7, line 38; (D19), page 8, line 32; (D20), page 10, lines 32-33). Hence, the person skilled in the art would have expected that citalopram is not crystallised easily, so that he would not have preferred crystallisation of the base over other known methods of purification. Moreover, there is no reason to believe that he would prefer to purify the base - which is an intermediate - rather than its salt, i.e. the final product. Nor does any other cited document point into this direction.

The comparative tests in documents (D30)(see the tables on pages 8 and 9) and (D31) show that crystallisation of the base more effectively removes the impurities of formula (II) as defined in present claim 1 as do the crystallisation of the salt or several other standard methods of purification.

5.4 Therefore, the subject-matter of claim 1 of the Main Request involves an inventive step. The same applies to the subject-matter of dependent claims 2-7 which relate to improved embodiments of the process of claim 1.

6. No grounds under Article 100(b) or (c) EPC were raised against the claims of the Main Request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent based on the amended Main Request (claims 1-7) filed during the oral proceedings before the Board and after any necessary consequential amendment of the description.

The Registrar: The Chairman:

M. Schalow P. Ranguis