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**Datasheet for the decision
of 10 September 2010**

Case Number: T 0457/07 - 3.3.02

Application Number: 99948905.7

Publication Number: 1117403

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:

mGluR5 antagonists for the treatment of pain and anxiety

Patentee:

Novartis AG, et al

Opponents:

Astra Zeneca AB
Grünenthal GmbH

Headword:

mGluR5 antagonists/NOVARTIS AG

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

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Keyword:

"All requests: inventive step (no): obvious alternative"

Decisions cited:

-

Catchword:

-



Case Number: T 0457/07 - 3.3.02

DECISION
of the Technical Board of Appeal 3.3.02
of 10 September 2010

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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
1 February 2007 concerning maintenance of the
European patent No. 1117403 in amended form.

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
L. Bühler

Summary of Facts and Submissions

- I. European patent No. 1 117 403 based on application No. 99 948 905.7 was granted on the basis of a single claim.
- II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and under Article 100(c) EPC for amendments that contain subject-matter extending beyond the content of the application as originally filed.
- III. The documents cited during the opposition and appeal proceedings included the following:
- (2) EP-A-0 703 218
 - (3) M.R. Young, et al., Brain Research 777, 161-169 (1997)
 - (5) M.E. Fundytus, et al., NeuroReport, vol. 9, no. 4, 731-735 (1998)
 - (8) EP-A-0 171 742.
- IV. The present appeal lies from an interlocutory decision of the opposition division pronounced on 14 November 2006 to maintain the patent in amended form on the basis of auxiliary request 1, filed during the oral proceedings before the opposition division.
- V. The opposition division came to the conclusion that the main request did not meet the requirements of Rule 57(a) EPC 1973 in view of the fact that the addition of three new dependent claims, which did not have any

counterparts in the granted patent, was neither appropriate nor necessary for overcoming a ground for opposition. The single claim of auxiliary request 1 met the requirements of Article 123(2) EPC, as mGluR5 antagonists were disclosed in claims 1 to 4 of the original application and, in view of the fact that the original application mainly related to mGluR5 antagonists, the feature "transdermal application" was unambiguously disclosed in the context of the mGluR5 antagonists. Moreover, the subject-matter of auxiliary request 1 did not extend beyond the content of the claims as granted and was therefore allowable under Article 123(3) EPC.

The invention as defined in auxiliary request 1 was sufficiently disclosed, as the opponents had failed to submit any evidence showing that there existed formulations for topical use which were not suitable for the mGluR5 antagonists as claimed and as paragraph [0049] of the contested patent provided sufficient information for the preparation of the transdermal compositions according to the invention.

Furthermore, the subject-matter claimed in auxiliary request 1 was novel vis-à-vis document (2), which did not specifically relate to mGluR5 antagonists.

As regards inventive step, the opposition division noted that the successful treatment of pain by transdermal application of an mGluR5 antagonist was plausible even if the contested patent did not contain direct evidence therefor. Starting from document (3) as closest prior art, which taught that mGluR1 rather than mGluR5 was involved in mediating nociception, the skilled person would be dissuaded from using mGluR5

antagonists for the treatment of pain. As a consequence, document (3), either alone or in combination with document (2), did not render the subject-matter of auxiliary request 1 obvious.

VI. Both the patentee (appellant-proprietor) and the opponents (appellant-opponent I and appellant-opponent II) lodged an appeal against that decision.

VII. With the statement of the grounds of appeal dated 11 June 2007, the appellant-proprietor filed a main request and auxiliary requests 1 and 2. The main request and auxiliary request 2 correspond to the main request and auxiliary request 1 of the decision under appeal. The independent claims read as follows:

(i) main request:

"1. The use of a mGluR5 antagonist in the manufacture of a pharmaceutical composition for transdermal administration, in the treatment of pain."

(ii) auxiliary request 1:

"1. The use of an mGluR5 antagonist in the manufacture of a pharmaceutical composition for transdermal administration, for the treatment of pain, whereby the mGluR5 antagonist is preferably a selective mGluR5 antagonist, whereby the mGluR5 antagonist exhibits preferably 100-fold greater activity at an mGluR5 receptor than at an mGluR1 receptor, or whereby the mGluR5 antagonist exhibits more preferably 200-fold greater activity at an mGluR5 receptor than at an mGluR1 receptor."

(iii) auxiliary request 2:

The sole independent claim is identical to claim 1 of the main request.

- VIII. In a letter dated 23 July 2010, appellant-opponent I withdrew his request for oral proceedings.
- IX. Oral proceedings were held before the board on 10 September 2010.
- X. In connection with inventive step, the appellant-proprietor's arguments can be summarised as follows: Document (5) was a scientific article investigating the function of group I metaboboric glutamate receptors (mGluR). The results obtained in various animal models were, however, inconsistent and even contradictory: thus, intrathecal application of mGluR1 or mGluR5 antibodies after DHPG administration in a rat model resulted in the attenuation of pain, whereas the formalin test, which was another established animal model in connection with pain, was negative. In view of these inconsistencies, the skilled person would dismiss document (5). Taken as closest prior art, however, it differed in at least three aspects from the subject-matter as claimed: (a) it did not relate to the therapeutic use of mGluR antagonists for the treatment of pain, (b) it did not describe the specific use of mGluR5 receptor antagonists, and (c) it did not refer to transdermal administration. Starting from document (5), in which the mGluR antibodies were applied intrathecally, the skilled person would not choose the transdermal route for the treatment of pain, as it was generally believed before the effective filing date of

the contested patent that the mGluR receptors were located within the central nervous system (CNS). As a consequence, the skilled person was dissuaded from replacing the tedious but effective intrathecal application by the transdermal route, which was considered to be unreliable in that the active agent supposedly had to cross the blood brain barrier in order to arrive at centrally located receptors. Only by learning that alleviation of pain could be obtained by blocking peripherally expressed mGluR5, which constituted the teaching of the contested patent, did the transdermal route become a favourable mode of administration. Document (8), which disclosed the transdermal application of centrally acting opioids, was not pertinent, either, as opioids were very specific compounds, known for their exceptional ability to cross the blood brain barrier, which could not be transferred to other active agents.

XI. In connection with inventive step, the arguments of appellant-opponent II can be summarised as follows:

Document (5) was a scientific paper relating to an investigation of the pain-relieving properties of mGluR1 and mGluR5 antibodies and therefore had a therapeutic implication. In view of the fact that the antibodies of document (5) were equivalent to mGluR1 and mGluR5 antagonists, the only difference between document (5) and the subject-matter of the present claims could be seen in the mode of administration. Starting from the teaching of document (5), the skilled person had good reasons for replacing the tedious and complicated intrathecal application by a more convenient mode of administration. For deciding whether

or not the selection of the dermal application involved an inventive step, the scientific theory therefor, i.e. the discovery of the peripheral location of the mGluR receptors involved, could not be taken into consideration, firstly because the subject-matter of the claims included every type of pain, i.e. peripherally and centrally processed pain, and secondly, because the skilled person knew that transdermally administered active agents could enter the CNS by crossing the blood brain barrier. In this context, reference was made to document (8), which disclosed the transdermal application of centrally acting opioids. It was emphasised that there was no evidence on file which demonstrated an equivalent, let alone an improved performance of transdermal application as compared with intrathecal application.

XII. The appellant-proprietor requested that the decision under appeal be set aside and a patent be granted on the basis of the main request or auxiliary request 1 filed with letter of 11 June 2007 or as a second auxiliary request that the appeal be dismissed.

Appellant-opponent I requested in writing that the decision under appeal be set aside and the patent be revoked.

Appellant-opponent II requested that the decision under appeal be set aside and that the European patent No. 1117403 be revoked.

Reasons for the Decision

1. The appeals are admissible.
2. Main request:
 - 2.1 As regards the basis for the amendments, sufficiency of disclosure and novelty, the board sees no reason to deviate from the decision of the opposition division. In view of the subsequent decision on inventive step (see point 2.2. below), it does not appear necessary to elaborate on these issues. As a consequence, the grounds of opposition according to Article 100(a) EPC in conjunction with Article 54 EPC and according to Article 100(b) and (c) EPC do not prejudice the maintenance of the patent on the basis of the present requests on file.
 - 2.2 Inventive step:
 - 2.2.1 The present invention relates to the treatment of pain by transdermal application of mGluR5 antagonists (see paragraphs [0005] and [0048] of the contested patent).
 - 2.2.2 Document (5) examines the role of group I mGluRs in nociceptive processing by intrathecally administering mGluR1 and mGluR5 antibodies to rat pain models. As correctly pointed out by appellant-opponent II (see point XI above), the mGluR antibodies according to document (5) are equivalent to mGluR antagonists in that they bind to and thus block the said receptors. The animal models used in document (5) allow the conclusion that mGluR5 antagonists are capable of alleviating certain types of pain, while other forms of

pain cannot be influenced by them (see page 731, first paragraph and page 735, paragraph bridging the two columns). Contrary to the appellant-proprietor's allegation, the passages cited above specifically mention mGluR5 antagonists as active agents. These diverging results obtained in the tests do not mean that the teaching of document (5) is inconsistent. The skilled person deduces therefrom that mGluR5 antagonists, like other analgesics as well, are selective in their pain-relieving activity and are therefore not suitable for every type of pain. In view of the fact that the subject-matter as claimed is not limited to specific forms of pain and thus includes those forms for which the mGluR5 antagonists of document (5) are effective, the finding that mGluR5 antagonists are selective in their anti-nociceptive activity is of no consequence. Moreover, animal models such as those according to document (5) are commonly used for demonstrating a therapeutic effect. Therefore, contrary to the appellant-proprietor's reasoning (see point X above) document (5) clearly comprises a therapeutic aspect. Therefore, document (5), which teaches that intrathecal administration of mGluR5 receptors can alleviate certain forms of pain, constitutes the closest prior art.

- 2.2.3 The contested patent does not include any tests in which the performances of interthecal and transdermal administration of an mGluR5 antagonist are compared. The contested patent mentions in paragraph [0038] the weak anti-hyperalgesic effect of intracerebroventricularly or intrathecally administered mGluR5 antagonists. However, no direct comparison is made with the corresponding transdermally applied

mGluR5 antagonists. In the absence of such data, the problem to be solved can be defined as the provision of a further mode of administration of an mGluR5 antagonist in the treatment of pain. The problem is solved by the subject-matter according to present claim 1, where the mGluR5 antagonist is administered by transdermal application. In the light of the disclosure in paragraphs [0038] to [0044], the board is satisfied that the problem defined above is plausibly solved.

- 2.2.4 Starting from the teaching of document (5), the skilled person had a strong motivation to replace the tedious and complicated intrathecal application by a more convenient mode of administration.

Assessing inventive step presupposes the acknowledgment of the technical teaching as it existed before the effective filing date of the contested patent. This means in the present case that the skilled person, trying to find an alternative for intrathecal application, was looking for a method of administration which allowed the active agent to enter the CNS, as it was believed at the time that the mGluR receptors, responsible for pain mediation, were located there. Knowing, however, that certain active agents such as opioids, which are able to cross the blood brain barrier, can enter the CNS by way of transdermal administration (see document (8)), the skilled person was not dissuaded from transdermal administration in order to solve the above problem. In this context, it is noted that the active agent according to claim 1 is not restricted to a particular chemical structure, but includes any agent capable of blocking mGluR5 receptor activity. The skilled person could therefore reasonably

expect to identify from the large group of possible candidates compounds having a chemical structure which allows them, even if only to a certain degree, to cross the blood brain barrier. As a consequence, the requirements of Article 56 EPC are not met.

The ultimate finding that the therapeutic effect can be attributed to peripherally rather than centrally located mGluR5 receptors cannot establish an inventive step. It merely provides a new explanation for a technical effect (alleviation of pain by transdermally administering an mGluR5 antagonist), which, as indicated above, is obvious in the light of the teaching provided by the prior art.

3. Auxiliary requests 1 and 2:

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request, since the term "preferably" does not restrict the scope of the claim. Claim 1 of auxiliary request 2 literally corresponds to claim 1 of the main request. As a consequence, the reasoning of point 2.2 for the main request applies *mutatis mutandis* to auxiliary requests 1 and 2. Therefore, the subject-matter as claimed in auxiliary requests 1 and 2 does not meet the requirements of Article 56 EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

N. Maslin

J. Riolo