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D E C I S I O N
of 25 January 2005

Case Number: T 0932/00 - 3.3.2

Application Number: 88112351.7

Publication Number: 0352361

IPC: A61K 31/485

Language of the proceedings: EN

Title of invention:

Method of treating patients suffering from chronic pain or
chronic cough

Applicant:

THE ROCKEFELLER UNIVERSITY

Opponent:

-

Headword:

Prevention of intestinal hypomotility/THE ROCKEFELLER
UNIVERSITY

Relevant legal provisions:

EPC Art. 54, 84, 123(2)

Keyword:

"Novelty (no) - use of known pharmaceutical combination for
avoiding a special side effect of one component"

Decisions cited:

G 0002/88

Catchword:

-



Case Number: T 0932/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 25 January 2005

Appellant:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 29 March 2000
refusing European application No. 88112351.7
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
J. H. P. Willems

Summary of Facts and Submissions

- I. European patent application No. 88 112 351.7 (publication No. 0 352 361) was refused by a decision of the examining division on the grounds of lack of novelty under Article 54(1) EPC.

Claim 1 of the main request before the examining division read as follows:

"The use of a pharmaceutically effective amount of an opioid analgesic or antitussive in combination with a pharmaceutically effective amount of an opioid antagonist substantially devoid of systemic antagonist activity when administered orally, for the manufacture of an oral composition useful for the treatment over a prolonged period of a patient in chronic pain or suffering from chronic cough; such a use being characterized in that:

(i)- said opioid antagonist is not an antagonist pro-drug;

(ii)- said opioid antagonist is systemically active when administered parenterally;

so as to provide an oral composition able to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility."

Claim 1 of the auxiliary request differed from the wording of the main request in the additional point

"(iii) the ratio by weight of the opioid analgesic or antitussive and the opioid antagonists ranges between 0.83:1 to 5:1;"

which was inserted before the words "so as to provide ...".

II. The examining division considered that the subject-matter of claim 1 of the main request was not novel since document

(6) US-A-4 457 933

disclosed compositions for oral use, comprising oxycodone (opioid analgesic) and naloxone (preferred antagonist in the present application) in order to avoid abuse, without affecting the analgesic effect.

The only difference which could be found between the subject-matter of claim 1 of the application and document (6) was that the present application disclosed that the known side effect of administering opioid analgesics, the onset of intestinal hypomotility, was avoided by administering the known composition because of the second component naloxone. However a side effect could not be considered as a medical indication as defined in decision G 2/88 "Friction reducing additive", OJ EPO 1990, 93. Additionally, the lack of side effect was inherently disclosed in the cited prior art.

With respect to the subject-matter of the auxiliary request, the examining division found that document (6) further disclosed the ratio between the opioid analgesic or antitussive and the antagonist suggested

in the single additional feature of claim 1. Thus, the subject-matter of the auxiliary request was not new over (6) either.

III. The appellant lodged an appeal against the decision of the examining division. Oral proceedings took place on 25 January 2005.

At the oral proceedings the appellant filed new sets of claims as main request and first and second auxiliary requests.

The wording of claim 1 of the **main request** is:

"The use of

 a pharmaceutically effective amount of an opioid analgesic or antitussive; and

 a pharmaceutically effective amount of an opioid antagonist for: the manufacture of an oral composition for the treatment over a prolonged period of a patient in chronic pain or suffering from chronic cough to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility; wherein:

(i)- said opioid antagonist is not an antagonist pro-drug and is substantially devoid of systemic antagonist activity when administered orally;

(ii)-said opioid antagonist is systemically active when administered parenterally."

A preferred opioid analgesic is oxycodone (claim 5) and preferred opioid antagonist is naloxone (claim 4).

In claim 1 of the **first auxiliary request** the subject-matter of claim 2 of the main request is added (additional wording in italics):

"The use of

a pharmaceutically effective amount of an opioid analgesic or antitussive; and

a pharmaceutically effective amount of an opioid antagonist for: the manufacture of an oral composition for the treatment over a prolonged period of a patient in chronic pain or suffering from chronic cough to provide systemic analgesia or central antitussive effect while simultaneously avoiding the onset of intestinal hypomotility; wherein:

- (i)- said opioid antagonist is not an antagonist pro-drug and is substantially devoid of systemic antagonist activity when administered orally;
- (ii)- said opioid antagonist is systemically active when administered parenterally;
- (iii)- *the pharmaceutically effective amount of opioid analgesic or antitussive is about 1.5 to about 100 mg per dosage unit; and
the pharmaceutically effective amount of opioid antagonist is from about 1 to about 18 mg per dosage unit.*"

Claim 1 of the **second auxiliary request** reads:

"The use of

a pharmaceutically effective amount of an opioid antagonist for: the manufacture of an oral composition for the treatment over a prolonged period of a patient

in chronic pain or suffering from chronic cough to avoid the onset of intestinal hypomotility in said patient to whom a pharmaceutically effective amount of an opioid analgesic or antitussive is administered to provide systemic analgesia or central antitussive effect; wherein

- (i)- said opioid antagonist is not an antagonist pro-drug and is substantially devoid of systemic antagonist activity when administered orally;
- (ii)- said opioid antagonist is systemically active when administered parenterally."

IV. The arguments of the appellant both in the written procedure and at the oral proceedings may be summarised as follows:

The subject-matter of the main request was new over the state of the art because the effect of the use of opioid antagonists to avoid intestinal hypomotility normally occurring with the long-term application of opioids was not disclosed in any cited document. From the teaching of the application in suit, it was for the first time possible for the manufacturer to write on the package insert of a medicament comprising an opioid that intestinal hypomotility would not occur when this medicament was used.

The teaching of document (6) was to use an oxycodone-naloxone composition to decrease the potential for oral abuse and thus for some kind of social control, and not to produce medical effects in the sense of curing a disease by means of the naloxone component.

Additionally, even if the effect of avoiding intestinal hypomotility by administering a composition according to document (6) occurred, it was a hidden effect.

Neither the patient nor the doctor would have recognised it, because the doctor knew about the danger of obstipation occurring with opiate medication and would in any case have prescribed some laxative together with the opioid.

As an indication that the effect was not recognised by all the persons skilled in the art, the applicant introduced the citation J.W. Simpkins et al, "Evidence for the Delivery of Narcotic Antagonists to the Colon as their Glucuronide Conjugates", J. Pharm. and Exp. Ther., Vol 244, No. 1, 195-205 (1), received for publication on 20 March 1987 (see the footnote on page 195, left column). It submitted that the facts and arguments in (1) even three years after the publication of document (6) (resulting from an application dated 24 November 1978 and being published 3 July 1984), led away from using naloxone-HCl to cope with the onset of intestinal hypomotility.

The wording of claim 1 of the first auxiliary request, additionally containing the features of claim 2 of the main request, still reduced the scope of its subject-matter, thus making it new in any case.

With respect to its second auxiliary request the appellant submitted additionally that intestinal hypomotility, even if it occurred as a side effect of the long-term administration of opioids, was to be seen simply as some disease condition to be treated medically. There should be no difference between such a

condition caused by another medication or for any other reason. The teaching of the application in suit could thus be the subject-matter of a second medical use claim.

Nevertheless, in case claim 1 of the main request did not meet the provisions of the EPC for formal reasons, the set of claims of the second auxiliary request was filed with a different wording for claim 1. This wording underlined in particular that it was the naloxone component referred to in the teaching of the application in suit that provided a new and hitherto unknown effect und thus made this teaching new over the state of the art.

- V. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, or alternatively on the basis of one of the auxiliary requests, altogether filed during today's oral proceedings.

Reasons for the Decision

1. The appeal is admissible.
2. Claim 1 of the main request and claim 1 of the second auxiliary request are based on original claim 9 and on page 4, paragraph 5, lines 10 to 12, of the description as originally filed; claims 2 to 6 correspond to original claims 10 to 12 and 15 to 16.

In the first auxiliary request, the only difference with respect to the main request is that claims 1 and 2 are formulated together in current claim 1 and the other claims are adapted accordingly.

The requirements of Article 123(2) EPC are consequently satisfied.

3. The wording "for the treatment over a prolonged period" is not defined exactly in the application as filed, but the person skilled in the art will find it to be in a range of several days to months or years. Thus this feature of the claimed use of an oral composition is very broad but not unclear, and there is no objection under Article 84 EPC.
4. In document (6) an orally administered oxycodone-naloxone composition is disclosed that acts as an analgesic (see claim 1).

Even if the features that the composition disclosed in the application as filed

- provides systemic analgesia
- while simultaneously avoiding the onset of intestinal hypomotility and
- said opioid antagonist is not an antagonist pro-drug and is substantially devoid of systemic antagonist activity when administered orally; and
- said opioid antagonist is systemically active when administered parenterally

are not specifically mentioned in (6), the combination of oxycodone and naloxone used in (6) must necessarily

exhibit these features, because in any case the same composition of oxycodone and naloxone is administered in the same way (orally) to the same group of patients suffering from pain.

Consequently, the applicant admitted that patients under medication using the oxycodone-naloxone composition of (6) plausibly would not suffer from opioid-induced constipation.

As for the feature "for the treatment over a prolonged period", the broad meaning of its wording makes it unsuitable for creating any difference between the subject-matter of the application in suit and the subject-matter of (6). Additionally, the problem to be solved in (6), namely providing analgesic activity by means of the oxycodone-naloxone mixture while decreasing the abuse potential (see column 2, lines 5 to 20, and column 4, lines 46 to 52) and exhibiting low physical dependence capacity (column 5, example 2), leads to the conclusion that the mixture referred to in (6) is intended for the "long-term treatment" of patients.

Thus, all features of the subject-matter of current claim 1 under investigation are exhibited by the composition disclosed in (6) and the teaching of the application in suit is not new over the teaching of document (6).

5. The appellant argued that the effect of naloxone added to a pharmaceutical composition of opioid to prevent intestinal hypomotility was a hidden effect that was not made available to the skilled person. It was not

described explicitly in the state of the art. Citation (1) indicated this situation by suggesting other possibilities for achieving this effect as many as three years later.

Therefore, a claim directed to such a use of naloxone was new.

However, this argument cannot succeed:

It is common general knowledge that strong opioid analgesics such as oxycodone or pentazocine can cause physical and psychic dependence in man. Therefore, the use of these analgesics on their own is considerably restricted. In order to overcome such restrictions, document (6) teaches administering these opioids in combination with naloxone and therefore allows a more extensive analgesic use (see column 1, lines 13 to 18 and lines 21 to 31).

Thus, document (6) clearly teaches treating patients suffering from serious pain with an opioid combined with naloxone.

Moreover, it is common general knowledge that the administration of opioid, as a side effect, normally gives rise to intestinal hypomotility.

The appellant admitted that the oral composition of document (6), when applied in its usual way, prevents this side effect.

Under these circumstances, the side effect inevitably and noticeable by the normally attentive physician does not occur when the known oral composition of document (6) is applied to treat pain in its usual way and, therefore, the effect of avoiding the side effect by co-administering naloxone to an opioid analgesic is in fact made available to the public per se.

The teaching that the presence of naloxone is the cause of the prevention of intestinal hypomotility remains as a scientific explanation of the effect being used by everybody treating pain by means of the composition set out in document (6); this explanation lying in the mind of the person carrying out the claimed invention and therefore being subjective rather than objective.

This finding cannot be altered, even if it was not expressly described in the state of the art that the onset of intestinal hypomotility did not occur when administering the known composition and even if a number of years later alternative ways enabling the skilled person to arrive at the same effect were discussed in the literature.

The appellant's argument that the doctor would in any case as a precaution prescribe a laxative together with an opioid was not supposed by any evidence and was not found prima facie likely by the board.

6. The subject-matter of the first auxiliary request exhibits the additional features vis-à-vis claim 1 of the main request that

"the pharmaceutically effective amount of opioid analgesic or antitussive is about 1.5 to about 100 mg per dosage unit; and the pharmaceutically effective amount of opioid antagonist is from about 1 to about 18 mg per dosage unit".

These given ranges of active substance per dosage unit are known from the table in column 2 of (6), lines 46 to 64.

7. Claim 1 of the second auxiliary request contains the same features as claim 1 of the main request, although the wording and order are somewhat different.

The strong tie between the oral administration of an opioid analgesic and the oral administration of the antagonist in order to cope with the side effect of the analgesic is in particular still present. Thus, the possibility of administering both active substances in one oral formulation is still contained in this claim and therefore its subject-matter is still anticipated by document (6).

8. Consequently, the board concludes that the subject-matter of the application in suit, with reference to the main request and the first and second auxiliary requests, is not new vis-à-vis the state of the art.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald