BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: T 541/89 - 3.3.2

Application No.: 79 300 516.6

Publication No.: 0 005 015

Title of invention: Use of a xanthine derivative in the manufacture of a medicament

Classification: A61K 31/52

D E C I S I O N
of 21 March 1991

Applicant: Beecham-Wuelfing GmbH & Co. KG

Opponent: Hoechst Aktiengesellschaft, Frankfurt

Headword: PVD/BEECHAM-WUELFING

EPC Art. 54 and 56

Keyword: "Novelty (yes) - neither explicit nor implicit disclosure of the matter claimed"
"Inventive step (no) - obvious solution"

Headnote

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammem | Boards of Appeal | Chambres de recours

Case Number : T 541/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 21 March 1991

Appellant : (Opponent)
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Decision under appeal :
Decision of Opposition Division of the European Patent Office dated 28 February 1989, posted on 23 June 1989, rejecting the opposition filed against European patent No. 0 005 015 pursuant to Article 102(2) EPC.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : A.J. Nuss
R.L.J. Schulte

Summary of Facts and Submissions

I. European patent No. 0 005 015 was granted with ten claims in response to the European patent application No. 79 300 516.6, filed on 29 March 1979 and claiming priority of an earlier application of 22 April 1978.

The first three claims of the patent as granted read as follows:

"1. The use of 1,3-di-n-butyl-7-(2-oxopropyl)xanthine for the manufacture of a medicament for increasing oxygen tension and contractility in ischaemic skeletal muscle.

2. The use of 1,3-di-n-butyl-7-(2-oxopropyl)xanthine for the manufacture of a medicament for the treatment of peripheral vascular disease.

3. The use as claimed in Claim 2 wherein the medicament is for the treatment of intermittent claudication."

II. The Appellant (Opponent) filed a notice of opposition against the patent, requesting revocation of the patent mainly on the grounds of lack of novelty, and lack of inventive step. During the opposition proceedings the Opponent cited, **inter alia**, the following documents:

(2) GB-A-1 441 562

(7) Therapie Woche 1972, pages 3 to 7.

III. The Opposition Division rejected the opposition, taking the view that vis-à-vis the cited documents the invention as claimed was not only novel, but also involved an inventive step, because the compounds mentioned in document (2) were said to increase the blood flow through skeletal muscle and that therefore, the compound used in the patent in suit was disclosed there only in connection

with vasodilation properties. This could not be regarded as implying an activity against peripheral vascular disease (PVD) since most compounds causing vasodilation of healthy arteria had no effect on ischaemic muscles. The fact that pentoxyphylline, another vasodilator used as a reference drug in document (2), was also known to have a PVD activity did not suggest however that any of the xanthines claimed there had both properties. Moreover, if anything, the man skilled in the art would have tried the most active of the compounds mentioned in this prior document viz. 1,3-di-n-butyl-7-(2-oxobutyl)-xanthine, another compound than that used in the patent in suit. Document (7) merely confirmed the efficacy of pentoxyphylline with respect to PVD.

IV. The Appellant lodged an appeal against this decision.

V. (i) Oral proceedings took place on 21 March 1991, in the course of which the Appellant contended that the xanthine compounds mentioned in document (2) were described as being suitable for the preparation of medicaments, which showed that said compounds were intended to be used to treat humans suffering from a disease. From the experiments described there - measurement of blood flow in healthy muscle and arterial and venous pO_2 (oxygen tension) - the man skilled in the art would have inferred that all these compounds were to be regarded as suitable for the treatment of muscle disorders due to blood flow disturbances. This implied that the therapy of peripheral vascular diseases, such as intermittent claudication, were the only relevant targets for the use of such medicaments. Therefore, the patent in suit did not disclose a new pharmaceutical use for 1,3-di-n-butyl-7-(2-oxopropyl)xanthine (compound A). Consequently, the object of the patent lacked

novelty. This conclusion was moreover fully in line with the declaration by Professor O. Hudlicka dated 22 February 1991.

In addition, the claimed invention did not imply an inventive step in view of document (7) from which it was known that pentoxyphylline, i.e. 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine (compound B) used as reference compound in document (2), possessed vasodilating and PVD-activity, e.g. against intermittent claudication. This compound was said to stimulate muscle blood flow. It was thus clear for the man skilled in the art that the target indication of the compounds mentioned in document (2) was the same a that of the reference compound pentoxyphylline.

(ii) The Respondent rejected these arguments because he considered that document (2) merely described the assessment of vasodilator activity in healthy skeletal muscle and not in ischaemic muscle. There existed thus no evidence to support the allegation that the compounds mentioned in document (2) would have been expected to increase oxygen tension and contractibility in ischaemic skeletal muscle or to be effective in the treatment of PVD. In addition document (7) concerned compound B and not compound A used in the patent in suit. Although mentioned in document (2), the latter compound was however only one of a series of compounds tested. There, the most active compound was said to be 1,3-di-n-butyl-7-(2-oxobutyl)-xanthine (compound C) and not compound A. Therefore, the man skilled in the art had no reason to consider compound A to be the most advantageous for treating ischaemic muscle.

Moreover, the submission of the Appellant did not take account of the technical prejudice that existed, at the priority date of the patent in suit, against the use of vasodilators in the treatment of PVD. According to Professor G. Trübestein's declaration dated 16 January 1990, a principle reason for this generally accepted prejudice in the cardiovascular field was that vasodilators operated in accordance with the "steal phenomenon" in ischaemic tissue, such as ischaemic skeletal muscle.

VI. The Appellant requested that the decision under appeal be set aside and the European patent No. 5 015 be revoked.

The Respondent requested that the appeal be dismissed and the patent be maintained as granted (main request); alternatively, by way of an auxiliary request, that the patent be maintained on the basis of Claims 1 to 8, filed with letter dated 21 March 1990.

VII. Claim 1, the only independent claim in accordance with Respondent's auxiliary request, reads as follows:

"1. The use of 1,3-di-n-butyl-7-(2-oxopropyl)xanthine for the manufacture of a medicament for the treatment of intermittent claudication."

Reasons for the Decision

1. The appeal is admissible.

2. There is no formal objection to Claim 1 of the (amended) set of claims in accordance with Respondent's auxiliary request. By deleting Claims 1 and 2 as granted, the former Claim 3 became the new main claim. There is adequate support for this limitation in the original application.

3. The patent in suit relates to the use of 1,3-di-n-butyl-7-(2-oxopropyl)-xanthine (compound A) in the manufacture of a medicament for treating peripheral vascular disease such as intermittent claudication.

4. The submission of the Appellant in regard to lack of novelty of the claims as granted is based on document (2).

It is stated in document (2) that "certain, hitherto unknown, 7-(oxoalkyl)-1,3-dialkyl xanthines are very effective in increasing the blood flow through skeletal muscle whilst at the same time showing a low toxicity". This statement follows a reference to prior art compounds of the same class known as vasodilators (see page 1, lines 6 to 16). Since increased blood flow is however the well known effect caused by dilation or widening of the blood vessels, it is clear that the compounds described in document (2) (i.e. a number of xanthine derivatives including compound A) concern nothing else than a series of vasodilators. Further statements in this specification and especially the tests serve to demonstrate among others the marked skeletal muscle blood circulation promoting effect and increased pO_2 values of these compounds, which, in the case of compound C, is found to be superior to that of the reference pentoxyphylline (compound B) (see page 1, lines 19 to 38 and Tables I and II).

It follows from the above that document (2) does not contain any information from which the man skilled in the art would have concluded that the known compounds, in particular compound A, would increase oxygen tension and contractibility in ischaemic skeletal muscle or would be effective in the treatment of peripheral vascular disease.

The declaration of Prof. O. Hudlicka dated 22 February 1991 to which the Appellant referred, is not considered as valid counter-evidence because this declaration is manifestly based on personal knowledge for which it has not been established that it was already acquired by Prof. Hudlicka at the priority date of the patent in suit, remote from the date of the declaration by almost thirteen years.

Consequently, the subject-matter of the claims as granted is novel.

5. Since it has been established above that document (2) does not provide any explicit or implicit disclosure of the teaching of the patent in suit, the Board is also of the opinion that this document does not represent the closest state of the art, but rather document (7), the only other document discussed at the oral proceedings. In view of the particular properties ascribed there to pentoxyphylline in the treatment of peripheral (obstructive) vascular diseases, the latter is actually more closely related to the subject-matter of the disputed patent than document (2) (see decision T 69/83, OJ EPO 1984, 357, in particular point 2 of the Reasons).

6. The technical problem to be solved in respect of document (7) is to be seen in providing the best possible alternative for pentoxyphylline (compound B).

In order to solve this problem, the patent in suit proposes the use of compound A for the manufacture of a medicament for the treatment of peripheral vascular disease such as intermittent claudication.

In view of the experimental results disclosed in the patent in suit (see in particular example 4), the Board is

satisfied that said technical problem is indeed solved by this proposal.

7. In document (7) the vasoactive compound 3,7-dimethyl-1-(5-oxo-hexyl)-xanthine, i.e. compound B, is described as an effective drug in the treatment of patients suffering from peripheral (obstructive) vascular diseases, in particular ischaemic arterial diseases such as intermittent claudication. The administration of this vasodilator leads to clearly improved flood flow in the peripheral muscle and the brain region with simultaneous increase in pO_2. It is also reported in this document that this drug is known to be more effective in ischaemic regions than in non-affected ones (see page 3, left column in toto; page 4, table 2, in particular point III; page 5, left column, first paragraph; page 7, left column, last paragraph).

It has never been disputed that document (2) was part of the state of the art for the man skilled in the art. Thus, when trying to find an alternative for compound B, he would certainly have noticed that in document (2) the very same compound is used for comparison in order to demonstrate the superior properties of a number of vasodilators belonging to the 7-(oxoalkyl)-1,3-dialkyl xanthines (see point 4 above). Although compound C is presented as the most active of these compounds, it is also stated in this document that the other compounds show equally marked pharmacological activity (see page 2, lines 21 to 24 and page 4, lines 25 and 26). The man skilled in the art would therefore have concluded that all the twelve compounds exemplified in the specification could be expected to be more potent vasodilators than compound B, having in particular increased blood flow properties in skeletal muscle and pO_2 values. Under these circumstances it must be assumed that he would normally have tried to find out whether or not these twelve

compounds are also superior to compound B in the treatment of peripheral vascular diseases, unless there existed at the priority date of the patent in suit a technical prejudice against the conducting of such routine investigation.

In support of such a prejudice, Professor Trübestein stated in his declaration that it was a generally held view (at the priority date) that vasodilators would not have been expected to increase oxygen tension and contractibility in ischaemic muscle or to be useful for the treatment of PVD (see point V(ii), last line). The Board does not deny that this might indeed be true in general, but certainly not as far as the specific compound B is concerned. Document (7) represents clear evidence that this is not necessarily true for all the vasodilators.

Therefore, the man skilled in the art would not have been discouraged but rather encouraged to carry out the very promising comparison tests on all twelve compounds disclosed in document (2) although he might not necessarily expect to detect for all these compounds a PVD activity superior to that of the reference compound B because he was of course well aware of the "steal phenomenon" mentioned in the declaration of Professor Trübestein. However, in view of what has been said in the preceding paragraphs, the man skilled in the art would not have given up the hope that, in spite of the difference in effect normally caused by vasodilators in healthy muscle and ischaemic muscle, the twelve compounds would not completely lose their superiority when tested in ischaemic muscle. He would thus have carried out appropriate comparison tests on all the compounds mentioned in document (2). As far as the result of these tests is concerned, the Board is of the opinion that under

these circumstances he could not have been surprised to find at least some compounds having activities comparable to that of compound B. The fact that the Respondent found one of them (compound A) having a better activity, and that another one (compound C) had a comparable PVD activity to that of compound B cannot be considered to be unexpected (see page 5, Table 1 of the patent in suit). The Respondent has submitted nothing in the course of the proceedings which would support the concept of a selection invention.

It follows from the above that none of the independent claims of the patent as granted involve an inventive step in the sense of Article 56 EPC.

8. The above considerations also apply to the treatment of intermittent claudication because, as admitted by the Respondent at the oral proceedings, this disease is merely a frequent form of obstructive vascular disease falling under the generic name PVD characterised by different pathological states. The Respondent's auxiliary request concerns thus a particular form or type of PVD simulated by experiment in the patent in suit. In the present case, the limitation to a particular degree in the status of PVD has however no bearing on the question of inventive step because the man skilled in the art would have tried to test all of the compounds mentioned in document (2) in view of their suitability for treating PVD in comparison to compound B known from document (7).

Consequently, Claim 1 of the auxiliary request does not involve an inventive step either.

Order

For these reasons, it is decided that:

1. **The decision under appeal is set aside.**

2. **The European patent No. 0 005 015 is revoked.**

The Registrar: **The Chairman:**

M. Beer P.A.M. Lançon