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D E C I S I O N
of 16 March 2001

Case Number: T 0922/98 - 3.3.2

Application Number: 93906266.7

Publication Number: 0643580

IPC: A61K 31/54

Language of the proceedings: EN

Title of invention:
Combinations of ACE inhibitors and diuretics

Applicant:
Merck & Co., Inc.

Opponent:
-

Headword:
Antihypertensive combination/MERCK

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 83, 123(2)

Keyword:
"Technical progression in relation to structurally less close or remote prior art vs inventive step in respect to the closest state of the art"
"Inventive step (no): obvious modification in the absence of any unexpected effects; Restriction of clinical trials under the Declaration of Helsinki; Extra effect"

Decisions cited:
G 0005/83, T 0121/81, T 0020/81, T 0143/94

Catchword:

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0922/98 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 March 2001

Appellant: Merck & Co., Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 23 March 1998 refusing European patent application No. 93 906 266.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 93 906 266.7, published under the PCT as WO 93/17 685, was refused pursuant to Article 97(1) EPC by a decision of the examining division posted on 23 March 1998; the decision was based on the main request and an auxiliary request, both filed during oral proceedings before the opposition division held on 17 February 1998. The two independent claims of the main request were worded as follows:

"1. A pharmaceutical formulation adapted for oral administration comprising a pharmaceutical carrier; enalapril maleate 20 mg and hydrochlorothiazide 6 mg.

3. The use of enalapril maleate 20 mg and hydrochlorothiazide 6 mg in the manufacture of an orally administrable medicament for the treatment of hypertension and congestive hart failure, by once a day administration."

Dependent claims 2 and 4 related to specific elaborations of the formulation according to claim 1 and the use according to claim 3 respectively.

The auxiliary request consisted of claims 1 and 2 of the above main request.

II. The stated ground for the refusal was that claim 1 did not involve an inventive step, having regard to the disclosure in citation (1), *viz* the publication by L. Andrén et al. in Journal of Hypertension, Vol. 1 Suppl. 2, 1983, pages 384 to 386. The substance of the reasoning given in the decision of the examining

division was as follows:

The closest state of the art, which was citation (1), disclosed, *inter alia*, pharmaceutical compositions comprising 6.25 mg of hydrochlorothiazide in combination with either 10 mg or 40 mg of enalapril. Claim 1 in the present application was directed to a closely related pharmaceutical composition comprising 6 mg hydrochlorothiazide in combination with 20 mg enalapril maleate, corresponding to 15.3 mg enalapril.

As the proportion of the enalapril component in the claimed composition fell within the range already suggested for the compositions disclosed in citation (1), the sole modification of the state of the art consisted in the minimal reduction of the proportion of the hydrochlorothiazide component. In the absence of any evidence showing that this obvious modification was unexpectedly associated with some improvement in the significant properties of the claimed composition, no inventive step could be acknowledged.

III. The appellant (applicant) lodged an appeal against this decision and requested oral proceedings. In the statement setting out the grounds of appeal it requested that a patent be granted on the basis of the annexed set of four claims which were identical with those of the main request refused by the impugned decision (cf. paragraph I above).

Further, the appellant submitted in the appeal statement, *inter alia*, that a head-to-head comparison of 20 mg (enalapril maleate)/6.25 mg (hydrochlorothiazide) *vs.* 20 mg/6.00 mg combinations for patent purposes alone was not permitted under the

"Helsinki Final Act" barring clinical trials which do not aim at a substantial alleviation of human illness.

IV. The board issued a communication to the appellant under Article 110(2) EPC, indicating that, if the appellant was indeed not allowed to conduct such clinical trials, it should seek to prove any alleged beneficial effect or advantage associated with the claimed invention in one or more other ways.

V. An oral hearing was held on 16 March 2001. Following a detailed discussion of the request submitted with the appeal statement, the appellant requested a short adjournment of the oral proceedings for deliberation. After resumption of the hearing the appellant withdrew his previous request and filed a new main request comprising two claims. Claim 1 corresponds to claim 3 of the main request refused by the impugned decision (cf. paragraph I above) with the following additions at the end of claim 1 indicated in bold italic letters below:

"1. The use of enalapril maleate 20 mg and hydrochlorothiazide 6 mg <.....> by once a day administration, ***having greater efficacy in reducing elevated blood pressure to normal levels than 20 mg enalapril maleate monotherapy."***

Dependent claim 2 corresponds to dependent claim 4 of the main request refused by the impugned decision.

VI. The appellant's submissions presented in the appeal statement and during the oral proceedings can be summarised as follows:

Although numerous combinations of various antihypertensive agents and hydrochlorothiazide were on the market before the priority date of the present application, none of these contained less than 12.5 mg hydrochlorothiazide. The skilled person would thus not consider that a combination of an ACE inhibitor, such as enalapril, and hydrochlorothiazide at an amount of 6 mg would have any chance of success as a marketed product. As the present application was directed to a clinical physician, a person with this qualification would consider actual marketed products to be the closest prior art rather than the disclosure of citation (1) describing the results of some clinical trials in patients with essential hypertension.

Even if the board were to accept the examining division's approach that citation (1) represented the closest state of the art, the teaching of this document would not be relevant enough to prejudice the inventive step of the claimed invention. Citation (1) disclosed five different combinations of enalapril and hydrochlorothiazide. While the ratio of enalapril (excluding the maleate) to hydrochlorothiazide in present claim 1 was 2.55, the ratios disclosed in (1) of enalapril with the lowest dose of 6.25 mg hydrochlorothiazide were either 1.6 (10 mg enalapril) or 6.4 (40 mg enalapril), and thus far removed from the ratio used in the claimed composition.

Moreover, the person skilled in the art would understand from the disclosure in (1) that a low dose of enalapril and a low dose of hydrochlorothiazide had a significant drawback in that potassium levels in subjects were reduced. This would have dissuaded him from trying combinations containing low doses of

hydrochlorothiazide.

The surprising findings, against the background of a prejudice in the art against very low doses of hydrochlorothiazide, that 6 mg of hydrochlorothiazide acted synergistically with enalapril, but was devoid of adverse side effects, justified the acknowledgment of an inventive step.

The appellant's additional finding that the combination of enalapril maleate and hydrochlorothiazide as defined in claim 1 had greater efficacy in reducing blood pressure to normal levels than monotherapy with enalapril alone using the same amount of enalapril maleate as present in the combination, was likewise neither disclosed nor obviously derivable from citation (1).

VI. The appellant requests, that the decision under appeal be set aside and that a patent be granted on the basis of the main request submitted during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. All references below to support for the present version of the claims in the application as filed are to the international application as published under the PCT (WO 93/17685):

claim 1 is based on claim 10 when dependent on claim 6 in conjunction with the disclosure on page 3, lines 13

to 16 and page 5, line 23 to page 6, line 3; dependent claim 2 finds its basis in Example 1, entry A.

2.1 The claims under consideration in the present decision are therefore acceptable as being supported by the disclosure of the application as filed and complying in this formal respect with the provisions of Articles 84 and 123(2) EPC.

2.2 The claims are drafted in conformity with the ruling of decision G 5/83 (OJ EPO, 1985, 64) and, accordingly, do not conflict with Article 52(4) or Article 57 EPC (see decision T 143/94, OJ EPO 1996, 430).

3. Present claim 1 relates to the use of a combination of 20 mg enalapril maleate and 6 mg hydrochlorothiazide in the manufacture of a medicament. Novelty was not at issue in the present case. Since none of the citations available to the board from the proceedings before the EPO discloses a medicament containing the above-mentioned components in the proportions as defined in present claim 1, the claimed subject-matter in the application under appeal is deemed to be novel within the meaning of Article 54(1)EPC.

4. The appellant submitted in the statement of grounds and during the oral proceedings that the skilled addressee of the present patent was a clinical physician, who would read the specification in the context of the nature of the products on the market at the priority date and who would, consequently, take actual marketed products containing a combination of an antihypertensive agent with hydrochlorothiazide to be the closest state of the art. The board cannot agree.

4.1 There may have been many reasons why a compound was not marketed at a particular time, but this cannot be interpreted as a sign of inferiority in any respect. In considering only marketed products to be representative of the closest state of the art, the appellant is concentrating on technical progress compared with the known products considered most effective. Technical progress is not a requirement for a patent under the European Patent Convention. It is true, of course, that technical superiority might be indicative of inventive step if it specifically relates **to the solution of the problem arising in respect of the closest state of the art**.

However, technical progress by comparison with marketed products representing less close or structurally remote prior art, as an alleged indication of inventive step, cannot be a substitute for the demonstration of inventive step with regard to some other, more relevant known products which are, for this very reason, termed the "closest" state of the art. (see eg decision T 181/82 "Spiro-Compounds"/CIBA-GEIGY, OJ EPO, 9/1984, 401).

4.2 According to the established jurisprudence of the Boards of Appeal (see "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition 1998, D. 3.1, pages 111 ff), the closest prior art for the purpose of objectively assessing inventive step is generally that which corresponds to the same or a similar use as the claimed invention and, at the same time, requires the minimum of structural and functional modifications to arrive at the claimed subject-matter. Whereas citation (1) disclosed that combinations of the ACE inhibitor enalapril and the diuretic

hydrochlorothiazide in proportions very closely related to those suggested in the application under appeal are effective in significantly reducing systolic and diastolic blood pressure, none of the marketed products referred to by the appellant contains the particular combination of the ACE inhibitor enalapril or a salt thereof with hydrochlorothiazide as the active agents and none of them has a hydrochlorothiazide content of less than 12.5 mg.

In view of the foregoing considerations it is beyond question that, in accordance with the finding of the examining division (see paragraph II above), citation (1) referred to in the European search report represents the closest available prior art to the subject-matter of the application.

4.3 More specifically, (1) discloses the use of five different combinations of E (enalapril) and H (hydrochlorothiazide) for the treatment of patients with mild or moderate hypertension by once a day administration (see especially page 384, right-hand column lines 9 to 10). In the left-hand column on page 385 of citation (1), under the heading "Results", it is stated: "The reduction in blood pressure was of the same magnitude in all the treatment groups and there was no significant difference in the blood pressure response between the five different combinations of E and H" : [group 1: E 10 mg and H 6.25 mg; group 2: E 10 mg and H 12.5 mg; group 3: E 10 mg and H 25 mg; group 4: E 40 mg and H 6.25 mg; group 5: E 40 mg and H 12.5 mg]. "Supine and standing heart rate were not significantly changed. The mean resting plasma levels of potassium was 4.1 mmol/l. There was a slight but significant decrease in potassium concentration in

group 1 (0.20 mmol/l; P < 0.05) and in group 3 (0.27 mmol/l; P < 0.05), while no significant change was observed in the other groups.

Plasma concentrations of sodium and uric acid remained unchanged in all groups."

4.4 In respect of the above-mentioned results reported in (1) the appellant seeks to rely on the argument that the skilled person would understand from the teaching of (1) that a combination of a low dose of enalapril and a low dose of hydrochlorothiazide had a significant drawback in that potassium levels in subjects were reduced. It has, however, failed to persuade the board that the problem was to find an improved pharmaceutical formulation overcoming the above-mentioned drawback.

4.5 Firstly, the authors of the clinical study reported in citation (1) clearly indicate that the decrease in plasma potassium observed in two of the five groups treated in (1) was "in no case of such a magnitude that potassium supplementation was considered necessary". What they do actually say in citation (1) in the context of the low dosage of hydrochlorothiazide used is that "a potential advantage with such low dosage is that dose-dependent side-effects, in particular the thiazide-induced ones may be minimized" (see (1) "Discussion" bridging the left-hand right-hand columns on page 385). The alleged drawback, if it really existed, could thus certainly not be considered as significant.

4.6 Secondly, the decrease in potassium concentration can neither be attributed, contrary to the appellant's assertion, to the combination of a low dose of

enalapril (10 mg) **and** a low dose of hydrochlorothiazide (6.25 mg), as used in (1) in the treatment of the group 1 subjects, nor to a low dose of enalapril **or** a low dose of hydrochlorothiazide. Thus, treatment of the group 3 subjects, with a combination comprising the same low dose of 10 mg enalapril and the maximum dose of hydrochlorothiazide used in these clinical trials (25 mg), caused a similar or even more distinct decrease in potassium concentration compared with the regimen used in the treatment of the group 1 subjects. On the other hand, treatment of the group 4 subjects, with a combination comprising the maximum dose of 40 mg enalapril and the minimum dose of hydrochlorothiazide used in these clinical trials (6.25 mg), did not provoke any significant change in potassium concentration at all.

4.7 Thirdly, and perhaps most important, even if such an alleged drawback had indeed existed, the appellant failed to provide any evidence showing that it had effectively been overcome by the provision of the claimed pharmaceutical formulation. Neither was an explanation given why such a small shift in the proportion of the hydrochlorothiazide component, ie from 6.25 mg to 6 mg, should have resulted in a significant improvement in, or significantly different properties of, the combination defined in present claim 1.

Nor is the argument that such evidence was unobtainable persuasive either. Apart from the fact that the "Declaration of Helsinki" (incorrectly called the "Helsinki Final Act" in the appeal statement) is only a recommendation by the World Medical Assembly rather than a law by which the applicant was bound, the

question whether or not certain experiments might be problematic for ethical reasons represents at most a difficulty such as may arise in connection with the testing or development of any invention and no particular allowance can be made to the appellant on this ground. Indeed, this is why the board suggested to the appellant in its communication that the alleged effect or advantage should be proved in one or more other ways, if clinical trials involving human subjects were indeed prevented as suggested by the appellant.

4.8 Consequently, the conclusion must be drawn that the additional advantages referred to by the appellant have not been properly demonstrated. Such alleged but unsupported advantages cannot be taken into consideration in the determination of the problem underlying the application (see T 20/81, OJ EPO 1982, 217).

5. In view of the above considerations, starting from (1) as representing the closest state of the art, the problem the invention as claimed in claim 1 seeks to solve may only be seen as that of providing a further orally administered pharmaceutical formulation for the treatment of essential hypertension and disorders associated therewith such as congestive heart failure, by once a day administration.

In order to solve this problem the appellant proposes the use of a pharmaceutical formulation comprising as the active ingredients a combination of enalapril maleate and hydrochlorothiazide in the particular proportions set out in claim 1 (20 mg enalapril maleate, corresponding to 15.3 mg enalapril and 6 mg hydrochlorothiazide). On the basis of the disclosure in

the application under appeal and the additional evidence submitted by the appellant during the oral proceedings, showing that treatment of a group of subjects with the combination of 20 mg enalapril maleate and 6 mg hydrochlorothiazide resulted in an average reduction of SDBP (supine diastolic blood pressure) of 7.3 mm Hg and SSBP (supine systolic blood pressure) of 11.5 mm Hg, the board is satisfied that the technical problem has been plausibly solved.

6. The skilled person seeking a solution to the stated technical problem in the state of the art would have learned from citation (1) that the combination of a low dose of enalapril (10 mg) with a very low dose of hydrochlorothiazide (6.25 mg), as used in (1), in the treatment of the group 1 subjects, was found to be at least as effective as combinations of higher doses of these drugs used in (1) in the treatment of the group 2 to group 5 subjects.

A closer inspection of the tabulated test results provided in Table 1 of (1) confirms that the group 1 treatment (10 mg E and 6.25 mg H) was even significantly more effective in reducing blood pressure than the group 2 treatment using 10 mg E and the double dose of 12.5 mg H [see group 1: SSBP = -22, SSDP = -14 *vs group 2:* SSBP = -19, SSDP = -10; the same is the case for standing systolic blood pressure (StSBP) and standing diastolic blood pressure (StDBP), see group 1: StSBP = -19, StSDP = -10 *vs group 2:* StBP = -20 StSDP = -7]. These results in (1) point the person skilled in the art to the existence of a synergistic effect between enalapril and hydrochlorothiazide at low doses in the range of about 6 mg H.

6.1 Consequently, on the basis of the beneficial results in the substantial reduction of systolic and diastolic blood pressure, achieved in (1) by using a low dosage regimen for both active ingredients, and the additional advantages referred to at the end of the disclosure in (1), namely that the use of such low dosage regimen may result in a minimisation of dose-dependent side-effects, in particular thiazide-induced side-effects, there existed absolutely no reason or incentive for a person skilled in the art to increase the low dose of hydrochlorothiazide used in (1) in combination with enalapril to any higher doses as used in the cited marketed products in combination with antihypertensive agents different from enalapril.

6.2 Once the solution to the stated problem by the provision of a combined formulation of a low dose of enalapril with a very low dose of hydrochlorothiazide became obvious to a person skilled in the art from the cited prior art, determination of the optimum proportion for either of the two active ingredients in the formulation would then be purely a matter of routine experimentation for the skilled practitioner.

Considering the closeness of the proportions of both enalapril and hydrochlorothiazide in the formulation used in claim 1 of the application under appeal to those in (1), there must be an expectation of the retention of their antihypertensive activity and efficacy to the same or at least to a similar degree. The minimal reduction of the proportion of 6.25 mg H to 6 mg H would certainly not be expected by one skilled in the art to have a significant effect on the antihypertensive activity of such combinations with enalapril.

6.3 With a view to providing a further argument in support of inventive step of the claimed solution over the prior art of (1), the appellant pointed during the oral proceedings before the board to the greater efficacy of the combination of 20 mg enalapril maleate and 6 mg hydrochlorothiazide in reducing elevated blood pressure to normal levels as compared to enalapril monotherapy with 20 mg enalapril maleate and argued that this property of the combined formulation used in claim (1) was not disclosed in the cited document. This property or effect, however, cannot form the basis of an inventive step either.

From the tabulated test results in Table 1 of (1) it is clearly derivable that the combination of **10 mg E and 6.25 mg H** is about as effective in reducing blood pressure to normal levels as the combination of the 4-fold dose of enalapril and the same low dose of hydrochlorothiazide, ie **40 mg E and 6.25 mg H**. In the board's judgment, these data provided in (1) necessarily imply to the skilled reader that the known combination of 10 mg E and 6.25 mg H used in (1) had likewise a greater efficacy in reducing elevated blood pressure to normal levels than enalapril monotherapy using the same dose of enalapril.

Even if one were nevertheless to accept that the greater efficacy of the combination of E and H defined in claim 1 compared with enalapril maleate monotherapy was neither explicitly nor implicitly derivable from the teaching of citation (1), this finding would merely amount to the detection of an extra effect (bonus) which was in the present case necessarily associated with the obvious solution of the stated problem (see points 6.1, 6.2 above). According to the consistent

jurisprudence of the boards of appeal of the EPO, such a bonus effect would, however, have to be disregarded in the evaluation of an inventive step (see T 21/81, OJ EPO 1983, 15).

6.4 Consequently, in the absence of any conclusive evidence showing that the minimal shift in the proportion of hydrochlorothiazide to the claimed area was unexpectedly associated with a beneficial effect, a significant advantage or an improvement in the relevant properties of the particular formulation used in claim 1, the conclusion must be drawn that the claimed use of the medicament defined in claim 1 shows only predictable effects and is therefore obvious.

6.5 During the oral hearing the appellant referred, in addition to citation (1), to the paper by A. J. Jounela et al, "Relation Between Low Dose of Hydrochlorothiazide, Antihypertensive Effect and Adverse Effects", published after the priority date of the application under appeal (11 March 1992) in Blood Pressure, 3, pages 231 to 235, 1994 [hereinafter referred to as citation (2)], suggesting that this document represented the general specialist knowledge about the effects of hydrochlorothiazide at the priority date. Even if this were accepted as being correct, it would not lead to a more favourable result for the appellant.

Although citation (2) teaches in Table IV on page 234 that treatment of subjects with a dose of 6 mg of hydrochlorothiazide as the sole active agent did not cause an increase in their plasma renin activity (PRA) and, moreover, mentions in the left-hand column on page 234 that 12.5 mg of hydrochlorothiazide proved to

be at the threshold of an effective antihypertensive response, this teaching is neither sufficient to demonstrate the existence of a possible prejudice in the art against using **a combination** of 20 mg E maleate and 6 mg H for the effective reduction of systolic and diastolic blood pressure in human subjects nor to deter the person skilled in the art from the claimed solution. Thus, the skilled person with the knowledge of citation (2) would also have known from citation (1), which had been published in 1983, that, in contrast to the effect of the diuretic hydrochlorothiazide as the sole medicament, the combination of the low dose of 10 mg E and the very low dose of 6.25 mg H exhibits a strongly synergistic effect in the treatment of hypertensive patients and is accordingly capable of effectively reducing diastolic and systolic blood pressure to normal levels in human subjects.

Consequently, the appellant's attempt to demonstrate, in reliance on the disclosure of (2), that a prejudice against the claimed invention had existed in the art or that the skilled person would have been diverted away from the claimed invention, must likewise fail for the reasons given above.

6.6 Finally, the board does not dispute that provision of the formulation defined in claim 1 for the treatment of hypertension may have been a commercial success. However, commercial success alone is not to be regarded as indicative of inventive step. In the present case, even if the board were to accept that the claimed success is derived from the features defined in claim 1 and not from other purely commercial causes, such commercial success cannot in itself be proof of

inventive step, when the technically relevant examination of the claimed subject-matter leads to a negative result (see Case Law of the Boards of Appeal of the EPO, 3rd edition 1998, D. 7.5, pages 141 to 142).

7. In conclusion, the claims of the appellant's current request do not fulfill the requirement of inventive step and are therefore not patentable (Article 52(1) in conjunction with Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

N. Maslin U. Oswald