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D E C I S I O N
of 22 May 2002

Case Number: T 0669/01 - 3.3.4

Application Number: 94919937.6

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IPC: A61K 37/36

Language of the proceedings: EN

Title of invention:
Use of human growth hormone for preoperative administration

Applicant:
Pharmacia AB

Opponent:
-

Headword:
Growth hormone/PHARMACIA AB

Relevant legal provisions:
EPC Art. 54

Keyword:
"Novelty - main, first and second auxiliary request (no)"

Decisions cited:
T 0279/93, T 0245/93

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0669/01

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 May 2002

Appellant: Pharmacia AB
SE-112 87 Stockholm (SE)

Representative: Tannerfeldt, Sigrid Agneta
Pharmacia AB
Patent Department
SE-112 87 Stockholm (SE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 8 January 2001 refusing European patent application No. 94 919 937.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: A. L. L. Marie
S. C. Perryman

Summary of Facts and Submissions

I. European Patent application No. 94 919 937.6 was refused by the examining division for non-compliance of the claims of the main and the auxiliary requests with the requirements of Articles 54 and 56 EPC. Both requests contained 7 claims and only differed in claim 1, which read in the case of the main request:

"1. Use of growth hormone (GH) for the manufacture of a medicament for preoperative administration in order to reduce protein loss."

Claim 1 of the auxiliary request was identical to claim 1 of the main request except for the addition of "...prior to the induction of the catabolic state." after "...protein loss."

II. The examining division considered that document (1) disclosed the use of growth hormone (GH) administered perioperatively to malnourished rats and its positive effect on the wound bursting strength. Since the healing of surgical wounds was directly related to the protein nutritional status of the animal (or patient), document (1) thus demonstrated the positive effect of the perioperative administration of GH on protein loss in malnourished animals. Document (2) showed that the perioperative administration of GH to normally nourished rats resulted in an increased wound breaking strength, which was likely to be due to an enhanced protein synthesis. The examining division further stated that claim 1 of both the main and the auxiliary requests did not exclude the possibility that patients receiving GH were malnourished before the operation, so that this feature could not be used as a distinction to

the disclosure of document (1).

III. An appeal was filed by the applicant against the decision of the examining division.

IV. A new main request as well as first and second auxiliary requests, each containing five claims, were submitted with the letter of 23 April 2002. Claim 1 of the main request read:

"1. Use of growth hormone (GH) for the manufacture of a medicament for preoperative and postoperative administration for the preparation of a patient for surgery where catabolic states develop after surgery in order to reduce protein loss prior to the induction of the catabolic state."

Claim 1 of the first auxiliary request only differed from claim 1 of the main request by the deletion of the expression "...prior to the induction of the catabolic state."

Claim 1 of the second auxiliary request corresponded to claim 1 of the first auxiliary request, to which the expression "...and for improvement in outcome following the surgery." has been added after "...to reduce protein loss."

V. As far as relevant for the present decision in view of Article 54 EPC, the appellant submitted the following arguments:

Document (1) concerned malnourished animals and could not show that the administration of GH prior to a catabolic state could be of therapeutic value, since

document (10) demonstrated that starvation caused a catabolic state similar to cancer cachexia, so that the malnourished rats described in document (1) were not GH-treated prior to the catabolic state, but after. The nature of the lost proteins as a result of malnourishment as in document (1) or confinement to bed and operation as in the present application was not the same.

In document (2) only the perioperatively GH-treated rats showed a positive effect, which was related to protein synthesis. To this extent, the teaching of document (2) differed from that of the present application which related the positive effect of GH to the inhibition of protein breakdown, ie to the reduction of protein loss. Document (3) did not concern the same medical indication (wound healing) as the present application (reduction of protein loss).

Document (4) did not anticipate the present invention, because GH was administrated post-operatively and the patients were given a hypocaloric diet. Document (4) taught the skilled person away from the subject-matter of the present application, since it stated on page 513 that there is no storage form of body nitrogen, so that the skilled person would not have considered that GH administration before the operation could be of any help.

VI. The Board issued a communication according to Article 11(2) of the rules of procedure of the Boards of appeal.

VII. The following documents are cited in this decision:

1. Y. Zaisen et al., Journal of Pediatric Surgery, 1990, Volume 25, pages 70 to 74

2. D.M. Hollander et al., Surgical Forum, 1984, Volume 35, pages 612 to 614

3. WO 91/11196

4. Z.-M. Jiang et al., Annals of Surgery, 1989, Volume 210, No. 4, pages 513 to 525

5. J. Gustafsson, Acta Pediatr. Scand. Suppl., 1989, Volume 362, pages 50 to 55

6. US 5,179,080

7. WO 87/04074

10. A.S. Whitehouse et al., Biochemical and Biophysical Research Communications, 2001, Volume 285, pages 598 to 602.

VIII. Oral proceedings were held on 22 May 2002.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of one of the sets of claims submitted on 23 April 2002.

Reasons for the Decision

Article 54 EPC

1. The differences between the main, first and second

auxiliary requests are directed to the avoidance of a possible clarity objection, which had already been alluded to in the communication under Article 11(2) of the rules of procedure of the Boards of appeal. The differences do not affect the subject-matter of the claims, so that these various sets of claims can be simultaneously considered for the purpose of novelty.

2. Document (1) deals with malnourished rats. Document (10), cited as an expert opinion, demonstrates that starvation (and *a priori* malnutrition) induces a catabolic state identical to that of cancer cachexia. Thus, the rats used in document (1), because of the fact that malnutrition was induced before GH administration, were already in a catabolic state similar to that induced by surgical operation before GH was administered. The GH administration in document (1) is hence neither pre- nor perioperative, but post-operative. Therefore, the teaching of document (1) is in a context different from that of the present sets of claims.

3. The definition of "*perioperatively*" in document (2) is different from that of the "*pre- and postoperatively*" as used in the present sets of claims. Indeed, "*perioperatively*" is defined on page 613 (lines 2 and 3) as meaning "*one day before the operation, the operation day itself and one day after the operation*", ie a period of three days. The present application (cf Examples 1 to 3), on the contrary, defines "*pre- and postoperatively*" as corresponding to a period of time including four or seven days before the operation, the day of the begin of the catabolic state and two or three days thereafter, ie altogether a period of time of 7 to 11 days. The skilled person using his/her

common general knowledge would assume that the effects developed by GH in a three-day-period are most probably not comparable with those of a 7 to 11 day-period. Thus, the overall teaching of document (2) is different from the subject-matter of the present sets of claims.

4. Document (3) is in the Board's opinion the most relevant prior art. Its purpose is to favour a very quick onset of healing and to reduce the incidence of post-surgical problems (page 1, lines 4 to 15; page 3, lines 19 to 24). Document (3) is thus in the same technical field and has the same purpose as the present application, which also aims at achieving an improved outcome for surgically operated patients (page 1, lines 8 to 12).

5. In order to achieve this purpose, GH is administrated, in document (3), to normally nourished rats in a period before and, optionally, after the operation.

6. The examples demonstrate that, in fact, GH administration is made pre- and postoperatively.

7. For instance, in Example 1, GH administration begins 7 days before surgery and continues until sacrifice, which occurs 2, 4 or 6 days after the operation, since the anastomoses are said on page 7 (last sentence) to be tested *in vivo* and *in situ* on the second, fourth or sixth postoperative day. GH has therefore been administrated during 9 to 13 days.

8. In Example 2, GH injections are made 4 days before operation and continued until the fourth post-operative day (page 14, lines 25 to 29), ie for an overall period of 8 days.

9. In Examples 3 and 4, GH is given one week before fracture and continued until testing, which occurs 40 days after fracture (page 15, line 28 to page 16, line 5).

10. Therefore, at least in the case of Examples 1 and 2, the pre-and postoperatively GH-administration of document (3), contrary to that of document (2) (cf supra, point 3), occurs over a period of time identical to that of the examples of the present application.

11. The teaching of document (3) is that GH, administrated pre- and postoperationally, has a positive influence on the outcome of the surgery.

12. This teaching is illustrated using various testing methods, which all relate to the field of surgery and represent real medical indications. In Examples 1 and 2, for instance, the left colon is resected and an end-to-end anastomosis made (page 7, lines 23 to 32). The effect of GH administration is then determined by the measurement of the bursting pressure, bursting wall tension and the bursting radius of the colonic anastomosis. In Examples 3 and 4, a standardized tibial fracture is produced and the influence of GH administration seen through the maximal loading, the stiffness and the maximum stress applied to the healed tibial bone. Another illustration of the influence of GH administration is the determination of the weight increase of the treated rats of Example 1 (cf Figure 1).

13. In the present application a different test is used to illustrate the effect of GH administration, namely the

reduction of protein loss (Tables 1 and 2, Figure 2) and constitutes the sole difference to the teaching of document (3).

14. This different test can be considered under two points of view.

15. It can first be considered as just another test, leading to and confirming the teaching already disclosed in document (3), ie the positive effect of GH administrated pre- and postoperationally on the outcome of surgical operations. Since a different test for the same medical condition cannot render a known process or use novel, the claims of the main, first and second auxiliary requests are already from this point of view not novel and do not comply with the requirements of Article 54 EPC.

16. On the other hand, it can also be considered, as the appellant does, as providing a scientific explanation of the mode of action of GH.

17. This is, however, contrary to the assumption of the appellant, not even the "discovery" of a new mode of action of GH, since Figure 1 of document (3) and the corresponding description from page 11 (line 22) to page 12 (line 8) demonstrate that the animals pre- and postoperatively GH-treated during 13 days show a weight increase as compared to the control, non-GH-treated animals and that their weight is during the whole test period above the value measured before GH administration. Due to the fact that the animals used in document (3) have been normally nourished (page 7, lines 6 to 8) and were not submitted to a special diet excluding, for instance, the contribution of the

protein metabolism to the weight increase, the skilled person would conclude that this weight increase reflects a stimulation of the overall anabolism of the GH-treated animals. Since proteins are important constituents of the body mass, a weight increase as the result of a stimulation of the overall anabolism can logically not correlate to a protein loss. On the contrary, the skilled person would conclude that, among other efects, the metabolism of protein has been shifted through GH administration in the direction of anabolism, this resulting in a positive nitrogen balance, ie in a reduction of the protein loss.

18. This conclusion, moreover, just reflects the common general knowledge of the skilled person on the properties of GH, which is to be found in the cited documents (1), (5), (6) and (7) which all characterize GH as an anabolic hormone favouring the protein synthesis, ie a hormone which, in the context of protein metabolism seen as a whole, results in a positive nitrogen balance.

19. This common general knowledge on the mode of action of GH is even more precisely explained by Figure 1 and Table 3 of document (4). Figure 1 shows that GH has been administrated to patients during seven days, starting one day after their operation, which produced a catabolic state. Table 3 mentions, among various parameters, the nitrogen intake, the nitrogen excretion and the nitrogen balance of control and GH-treated patients, thus allowing one to determine whether the influence of GH administration is on the protein synthesis (anabolism), or protein breakdown (catabolism) or both. The conclusion is that for the control, non GH-treated patients the daily values of

the nitrogen uptake and nitrogen excretion remain nearly constant over the test period and result in a negative nitrogen balance. The control patients are thus in a state, in which the catabolism of protein is stronger that the anabolism. This results in a protein loss. In the case of the GH-treated patients, GH administration does not modify the values of the nitrogen uptake over the test period, but from the third post-operative day onwards constantly diminishes the values of the nitrogen excretion, resulting on the fifth post-operative day in a positive nitrogen balance. This shows that GH administration stops the catabolic state caused by surgery by acting against the catabolism of protein and hence **reduces the protein breakdown and protein loss**. In this case, if the protein metabolism is seen as a whole, the decrease of the protein catabolism and the maintenance of the protein anabolism result in a positive nitrogen balance and in the fact that more proteins are synthesized than destroyed. This leads to the conclusion mentioned in documents (1), (5), (6) and (7) which characterize GH as an anabolic hormone favouring the protein synthesis (cf supra, point 18).

20. Therefore, the feature "*in order to reduce the protein loss*" is nothing else than the well-known common general knowledge of the skilled person on GH and cannot contribute to the novelty of the claims of the present requests which also from this point of view do not meet the requirements of Article 54 EPC.

21. Furthermore, the established case law of the Boards of appeal has already considered in decisions T 254/93 (EPO OJ 1998, 285) and T 279/93 (12 December 1996) the situation where the only difference between an

application (or a patent) and the prior art is the "discovery" of a new property of a known compound or of the explanation of the effect of a known compound.

22. In decision T 279/93 (cf supra, point 17) novelty was denied, since the new property did not lead to a new use, so that the claims did not teach the skilled person to do something which would not have been done without knowing the content of the patent. The same situation applies to the present case, since the skilled person is not taught by the application to do something which is different from the teaching of document (3) in order to achieve the same purpose.

23. Similarly, in decision T 245/93 (cf supra, point 17), the Board concluded that "the mere explanation of an effect obtained when using a compound in a known composition, even if the explanation relates to a pharmaceutical effect which was not known to be due to that compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect when applying the known process" (point 4.8). In the present case, document (3) demonstrates the same effect as the present application in relation to the same use of the same compound, ie the positive influence of GH administration on the outcome of surgical operation.

24. Therefore, the claims of the main, first and second auxiliary requests do not comply with the requirements of Article 54 EPC.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U.Kinkeldey