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D E C I S I O N
of 14 June 2000

Case Number: T 0985/95 - 3.3.4

Application Number: 88901571.5

Publication Number: 0300021

IPC: A61K 37/38

Language of the proceedings: EN

Title of invention:
A process for treating infertility and an agent for use in the process

Patentee:
Novo Nordisk A/S

Opponent:
Pharmacia Aktiebolag
Applied Research Systems ARS Holding NV

Headword:
Treatment of infertility/NOVO NORDISK A/S

Relevant legal provisions:
EPC Art. 123(2), 84, 83, 54, 56

Keyword:
"Main request: clarity (yes); added subject-matter (no); novelty (yes); inventive step (yes)"

Decisions cited:
T 0694/92

Catchword:
-

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Case Number: T 0985/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 14 June 2000

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 13 October 1995 rejecting the opposition filed against European patent No. 030 021 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division maintaining European patent No. 0 300 021 (application No. 88 901 571.5) in amended form. The patent had been granted on the basis of 6 claims and has the title: "A process for treating infertility and an agent for use in the process". Claim 1 as granted read as follows:

"1. Use of a composition comprising a combination of growth hormone and gonadotrophins for the production of a medicament for treatment of infertility in human beings or higher animals."

Dependent claims 2 to 5 related to specific embodiments of the medical use of claim 1. Claim 6 was directed to a process for the production of a medicament.

II. The parties referred to following documents:

(1) Wilson C.A. et al., J. Endocrinology, Vol. 104, pages 179-183 (1985);

(2) Xiao-Chi Jia et al., Endocrinology, Vol. 118, pages 1401 to 1409 (1986);

(3) Adashi E.Y. et al., Endocrine Reviews, Vol. 6, pages 400 to 420 (1985);

(8) Davoren B.J. et al., Am. J. Physiol., pages E26-E32 (1985);

(10) Adashi E.Y. et al., Endocrinology, Vol. 117, pages 2313 to 2320 (1985);

Exh.(1) Hull G.R. et al., British Medical Journal, Vol. 291, page 1693 to 1697 (1985);

Exh.(3) Cassar J. et al., Brit. J. Obst. Gyn., Vol. 87, pages 337 to 339 (1980);

Exh.(4) Yusoff Dawood M. et al., Fertility and Sterility, Vol. 38, pages 415 to 418 (1982).

Ref.(1) Marshall J.C. et al., New England J. Med., Vol. 315, pages 1459 to 1468 (1986);

Ref.(2) Bronson F.H., Endocrinology, Vol. 118, pages 2483 to 2487 (1986);

Ref.(3) Leyendecker G. et al., J. Reprod. Fert., Vol. 69, pages 397 to 409 (1983);

Ref.(4) Advis, J.P. et al., Endocrinology, Vol. 108, pages 1343 to 1352 (1981);

Ref.(10) European Pharmacopea 1986, page 508.

III. With a letter dated 6 June 2000, the respondent (patent proprietor) filed claims 1 to 7 of a main request, claims 1 to 6 of auxiliary request 1 and claims 1 to 7 of auxiliary 2 in replacement of any previous claim requests. A new main request was submitted during the oral proceedings held on 14 June 2000, whose claims 1 and 2 (amendments over the corresponding granted claims are in bold), read as follows:

"1. Use of a composition comprising a combination of growth hormone and gonadotrophins for the production of a medicament for treatment of infertility in **mature** human beings or **mature** higher **female mammals**, **said growth hormone being specific to the species in question**."

"2. Use of a composition comprising a combination of growth hormone and gonadotrophins for the production of a medicament for treatment of infertility in **mature** human beings or **mature** higher **female mammals**, **by administration of individually adapted amounts effective to enhance ovarian follicle and oocyte maturation in said mammal or human being, said growth hormone being specific to the species in question**."

IV. As regards the main request, the arguments submitted by the appellant (opponent 02) were essentially as follows:

Article 123(2) EPC

- There was no basis in the application as filed for the term "mature" in claims 1, 2 and 7, nor for the wording in claim 2 "to enhance ovarian follicle and oocyte maturation".

Article 84 EPC

- The term "mature" in claims 1, 2 and 7 was not clear.

Sufficiency of disclosure

- The claimed medical use was not effective for treating infertility due e.g. to primary ovarian failure but only infertility due to secondary ovarian failure (hypogonadotrophic hypogonadism)(see patent in suit, page 3, lines 27 to 35). Therefore, the claimed treatment of infertility could not be achieved across the **whole** range of "infertility" stated in claim 1 and embracing all the causes of infertility listed in Table I of Exh.(1), contrary to the rationale set out in decision T 694/92 (OJ EPO 1997, 408).

Novelty

- The claimed medical use was not novel over document (1) disclosing the use in vivo of growth hormone together with gonadotrophins to induce ovulation in immature (prepubertal) female rats, which went from an infertile state to a fertile one.

Inventive step

- It was obvious to try to improve with a reasonable expectation of success the treatment of infertility based on gonadotrophins alone by combining gonadotrophins with growth hormone (GH), on the following grounds:

  Document (1) taught that pregnant mare serum gonadotrophin (PMSG) induced ovulation in prepubertal rats weighing less than 60 g only if these had previously been treated with GH. The administration of PMSG was associated with hypersecretion of luteinizing hormone (LH).

Therefore, the skilled person would expect that the combination of gonadotrophins with growth hormone (GH) would achieve the same effect in mature female with hypothalamic amenorrhea, having regard to the fact that the physiological status of an immature (prepubertal) female rat and that of a mature female with hypothalamic amenorrhea were identical (in both cases there was a lack of gonadotrophin releasing hormone (GnRH) signal from the brain being delivered to the anterior pituitary (see Ref. (1) to (3) and (10)).

This equivalence of physiological statuses made the immature (prepubertal) female rat a widely accepted animal model for studying infertility in mammals.

- Moreover, several documents of the prior art suggested a synergistic effect between GH and the follicle-stimulating hormone (FSH), which is a gonadotrophin, in the stimulation of the ovarian function. Ref. (4) taught that GH stimulated the ovarian function. Document (2) showed that GH increased gonadotrophin-stimulated differentiation of ovarian granulosa cells. Document (3) disclosed a synergistic effect of the insulin-like growth factor I/somatomedin C (IGF-I/Sm-C) on FSH. The same effect was disclosed by documents (8) and (10). IGF-I/Sm-C was known to be GH-dependent (see document (8)).

IV. The submissions provided by the respondent in support of the claims of the main request can be summarized as follows:

Article 123(2) EPC

- There was a basis in the application as filed for the term "mature" in the claims of the newly filed main request as well as for the wording "to enhance ovarian follicle and oocyte maturation".

Article 84 EPC

- The term "mature" in claims 1, 2 and 7 had to be understood as "sexually mature" and was clear to the skilled person.

Sufficiency of disclosure

- The above method could also be used for in vitro fertilisation (patent in suit, page 3, line 38) indicating a broader number of female pathological conditions (see Exh. (1)).

Novelty

- The wording in the claims "said growth hormone being specific to the species in question" rendered the claims novel over document (1).

Inventive step

- While the (prepubertal) female rat was a widely accepted animal model for studying the mechanisms involved in the onset of puberty, it was not used for studying infertility in mammals. Facts relating to inducing puberty in immature rats had no relevance to the treatment of infertile mature sexually active rats. The adult infertile state

was not equivalent to the prepubertal state. Growth hormone (GH) did not play the same role in both states. In the prepubertal state, the plasma concentration of GH first raised then dropped when maturation was reached. All the cited documents dealt with investigations on factors (including GH) involved in pubertal development, not with unwanted pathological infertility.

- As regards document (1), Table (1) of this document showed that GH potentiated PMSG poorly, while Table (2) thereof showed that GH had no effect in increasing the number of human chorionic gonadotrophin (hCG) binding sites. These experimental results would have dissuaded the skilled person from combining gonadotrophins with GH.

- Ref. (4) and documents (1),(2) and (3) gave contradictory information about the effect of GH on FSH in stimulating the ovarian function.

- There was a prejudice against the combined use of gonadotrophins with GH because it was known that even in cases of GH deficiency, a successful ovulation could be induced with gonadotrophins alone (see Exh.(3) and (4)).

V. The appellant (opponent 02) requested that the decision under appeal be set aside and that European patent No. 0 300 021 be revoked.

The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request

submitted in the oral proceedings or auxiliary requests 1 or 2 filed with the letter dated 6 June 2000.

Reasons for the Decision

1. The appeal is admissible

Main request

Article 123(2) and (3) EPC

2. The wording "mammal" in claims 1, 2 and 7 finds a basis on page 1, line 2 of the application as filed. Although not stated expressis verbis, the term "mature" in these claims is implicit from the whole context of the application as filed (page 5, lines 23 to 24) referring to infertility of **couples** ("Infertility among couples is estimated to have an annual incidence of 1.2 couples for every 1,000..."): infertility of necessity occurs in spite of sexual maturity and unprotected sexual activity. It is also implicit that the patients subjected to the claimed infertility treatment (see the Examples in the application as filed) are "mature" since they are aged 35, 39, 39 and 38. The wording "specific to the species in question" in claims 1, 2 and 7 finds a basis on page 5, lines 18 to 19 of the application as filed.

The expression "by administration of individually adapted amounts effective to enhance ovarian follicle and oocyte maturation in said mammal or human being" in claim 2 finds a basis on page 5, lines 13 to 14 and page 6, lines 7 to 9 of the application as filed. The

wording "on the stimulation of ovarian function" in claim 5 is based on page 4, line 15 of the application as filed. All these amendments are restrictive in nature so that the requirements of Article 123(2), (3) EPC are fulfilled.

Article 84 EPC

3. The term "mature" is clear and means "sexually mature", as can be deduced from the application as filed relating to females who fail to become pregnant in spite of sexual maturity and unprotected sexual activity (see page 5, lines 23 to 24: infertility of couples; see also the Examples in the application as filed, wherein the patients are aged 35, 39, 39 and 38).

Sufficiency of disclosure

4. The appellant maintains that the claimed treatment of infertility cannot be achieved across the whole range of "infertility" stated in claim 1, contrary to the rationale set out in decision T 694/92 (loc. cit.). However, in the board's view, unlike the situation dealt with in this decision, there is sufficient guidance in the patent in suit for which infertility situations the claimed medical use will certainly provide the intended effect. The claimed medical use is effective for treating infertility due to secondary ovarian failure (hypogonadotrophic hypogonadism)(see patent in suit, page 3, lines 27 to 35). This information enables the skilled person to select among all the causes of infertility listed in Table I of Exh. (1) those where the claimed medical use is likely to be successful. Therefore, the requirements of

Article 83 EPC are fulfilled.

Novelty

5. Document (1) discloses the use in vivo of **bovine** growth hormone (see page 180, l-h column, under the heading "Treatments"), together with gonadotrophins to induce ovulation in immature (prepubertal) female **rats**. The wording in claims 1, 2 and 7, however, requires inter alia that the growth hormone should be specific to the species in question. The subject-matter of claims 1, 2 and 7 is therefore novel over document (1), wherein bovine growth hormone is administered to rats. This conclusion also applies to claims 3 to 6 by virtue of their dependency on claim 1.

Inventive step

Introduction

6. The ovarian function of higher mammals and humans is regulated by pituitary sex hormones, called gonadotrophins. These include FSH which causes follicle maturation, and LH which causes ovulation (see patent in suit, page 2, lines 10 to 12).

Closest prior art

7. It is agreed by the parties that the closest prior art underlying the claimed subject-matter is represented by treatments of infertility with gonadotrophins alone, as referred to in the patent in suit (see page 2, lines 45 to 49) and the board agrees as well. It is also stated on page 2, lines 50 to 54 that the treatment of infertility with injections of gonadotrophins was

affected by a series of drawbacks such as, inter alia, failure by a percentage of the treated women to become pregnant and risks due to overstimulation, such as formation of ovarian cysts. The problem the patent in suit purports to solve is to provide an improved treatment of infertility devoid of the drawbacks of the previous treatment with gonadotrophins alone. Comparative Examples 1, 3 and 4 of the patent in suit show a superior fertilization effect and an improvement of the chance of pregnancy upon treatment with a combination of gonadotrophins and GH versus the treatment with gonadotrophins alone. The board is thus satisfied that this problem has been solved by the medical use stated in claim 1.

8. Therefore, it remains to be decided whether or not the proposed solution to this problem is obvious in the light of the cited prior art.

9. The appellant argues that it was obvious to combine gonadotrophins with GH for the treatment of infertility in the light of document (1) and of the fact that the immature (prepubertal) female rat was a widely accepted animal model for studying infertility in mammals. The board observes that Table (1) of document (1) relates to the ovulatory effect of various hormones on rats weighing less than 60 g previously treated with PMSG (equivalent to gonadotrophins). This Table shows that LH, FSH, ACTH (1-39) (porcine corticotropin), its fragment ACTH (1-24) and corticosterone **all** perform better than GH in potentiating PMSG. Administration of GH with PMSG thus achieves one of the worst results (only 12 out of 22 rats ovulate). Therefore, in the board's view, even if one accepts the appellant's "rat model for studying infertility", the conclusion cannot

be drawn that document (1) encourages the skilled person to combine gonadotrophins with GH. Further, in another experiment aiming at studying the effect of PSMG, GH and corticosterone on the ovarian function (see Table (2) of document (1)), the number of hCG binding sites in ovarian tissue is measured. It turns out that the addition of GH to PSMG has no effect in increasing the number of hCG binding sites in ovarian tissue (PMSG alone = 29.59 cpm x 10^{-2}; PSMG + GH = 29.36 cpm x 10^{-2}). In the board's opinion, this experimental result further dissuades the skilled person from combining gonadotrophins with GH.

10. The appellant maintains that several documents of the prior art (see section II above) suggest a synergistic effect between GH and the gonadotrophin FSH in the stimulation of the ovarian function. The board, however, observes that Ref. (4) (see page 1350, paragraph bridging l-h and r-h columns: "the present results indicate a direct effect on the ovary") suggests a **direct** effect of GH on FSH in stimulating the ovarian function of rats. Document (3) teaches that said effect occurs **indirectly** via IGF-I/Sm-C for rats (see page 407, r-h column; see also page 409, bottom of l-h column: "Sm-C/IGF-I synergized with FSH in the induction of progesterone biosynthesis by granulosa cells") and pigs (see page 408, passage bridging l-h and r-h columns). There is a statement in document (3) that IGF-I/Sm-C stimulates swine granulosa cell **of its own,** i.e. without the help of FSH (page 408, bottom of r-h column). Further, according to document (2) (see Figure 1), GH **potentiates** FSH in increasing the number of hCG receptors, while document (1) (see paragraph 9 supra) teaches that the addition of GH to FSH (PSMG) **has no effect** in increasing the number of hCG binding

sites in ovarian tissue. In the board's view, contradictory statements of this kind reflect the complexity of the prior art underlying the claimed subject-matter, which prior art does not unambiguously suggest an improved effect between GH and FSH in the stimulation of the ovarian function in prepubertal animals, much less in mature mammals or human beings suffering from infertility.

11. In conclusion, the addition of GH to the already known anti-sterility medicament gonadotrophins to obtain an improved effect is suggested nowhere. The medical use of claims 1 to 6 involving gonadotrophins and GH and the process for the production of a medicament comprising gonadotrophins and GH of claim 7 satisfy the requirements of Article 56 EPC.

12. Since the board is satisfied that the claims of the main request meet the requirements of the EPC, no need arises to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the main request submitted in the oral proceedings.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey