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D E C I S I O N
of 27 June 2005

Case Number: T 1100/04 - 3.3.4

Application Number: 00203295.1

Publication Number: 1099445

IPC: A61K 38/16

Language of the proceedings: EN

Title of invention:
Treatment of neuromuscular disorders and conditions with different botulinum serotype

Applicant:
Allergan, Inc.

Opponent:
-

Headword:
Botulinum toxin type B/ALLERGAN INC

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and auxiliary request: inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1100/04 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 June 2005

Appellant: Allergan, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 April 2004 refusing European application No. 00203295.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
G. E. Weiss

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (appellant) against the decision of the examining division to refuse under Article 97(1) EPC European patent application EP 00 203 295.1 with publication number EP-A-1 099 445, a divisional application of EP 94 920 705.4 (publication number EP-A-0 702 561). The patent application has the title: "Treatment of neuromuscular disorders and conditions with different botulinum serotype".

II. The examining division decided that the claims of the main request and those of the first auxiliary request then on file lacked an inventive step.

III. With the statement of grounds of appeal the appellant identified as **Main Request** the set of claims (1 to 8) of the main request refused by the examining division, of which claims 1 and 2 read as follows:

"1. The use of botulinum toxin type B for the manufacture of a medicament for the treatment of a neuromuscular disorder or condition in a patient to whom botulinum toxin type A has previously been given and said patient has experienced a loss of clinical response to the administered botulinum toxin type A."

"2. The use of botulinum toxin type B for the manufacture of a medicament for the treatment of a neuromuscular disorder or condition in a patient to whom botulinum toxin type A has previously been given and said patient has developed neutralizing antibodies to the administered botulinum toxin type A."

IV. Oral proceedings were held on 27 June 2005, during which the appellant filed an **Auxiliary Request** (claims 1 to 7), differing from the set of claims of the main request in that it no longer included claim 2 thereof and renumbering.

V. The following documents are cited in the present decision:

(D2) Ludlow C.L. et al., New England Journal of Medicine, Vol. 326, No. 5, pages 349-350 (30 January 1992);

(D5) Borodic G.E. et al., Ophthalmic Plastic and Reconstructive Surgery, Vol. 9, No. 3, pages 182-190 (1993);

Annex (A) Moyer E. et al. in "Neurological Disease and Therapy. Therapy with Botulinum", Jankovic J. Editor, pages 71-85 (1994);

Annex (B) Spanoyannis A. et al., AACPDM Abstracts, Abstract No. SP:8, pages 33-34 (1998);

Annex (C) Carruthers A. et al., Dermatol. Surg., Vol. 26, No. 3, pages 174-176 (2000);

Annex (D) Tsui J.K.C. et al., Neurology, Vol. 45, pages 2109-2110 (1995);

Annex (F) Blasi J. et al., Nature, Vol. 365, pages 160-163 (9 September 1993).

VI. The appellant's arguments were essentially as follows:

- Document (D2) represented the closest prior art. This document related to solving the same problem of loss of clinical response upon treatment with Botulinum toxin type A as recited in present claim 1. However, the adopted solution in this document, namely switching to Botulinum toxin type F, achieved poor results, *inter alia* because of short duration of action despite the massive dose. The objective problem underlying the present invention was thus the provision of an improved treatment for these patients. The non obvious solution as claimed was switching to Botulinum toxin type B.

- There was a complete lack of human clinical experience with type B toxin until 1995, i.e., two years after the priority date of the present application (1993) (see Annex (D)). It thus was completely unknown whether or not Botulinum toxin type B would have any therapeutic efficacy in humans (see Annex (A), page 81, under the heading "Clinical uses of Botulinum toxin type B").

- In vitro histological experiments with rabbits were not predictive of how Botulinum type B toxin would behave in humans. Therefore, it was not safe to inject a human with Botulinum toxin type B, also because of the high variability between species.

- There were significant differences in the activities and structures between the various Botulinum toxin serotypes (see Annexes (A), (F) and (C)).

– Document (D5) did not describe any assay for measuring the resistance to Botulinum toxin type A. There was thus no expectation of success or evidence that Botulinum toxin type B would work also in the presence of neutralizing antibodies.

– There was evidence that antibodies generated against Botulinum toxin type A could cross-react against Botulinum toxin type B, thereby questioning the clinical efficacy of Botulinum toxin type B.

Auxiliary request

– Neither document (D2) nor document (D5) described any assay for measuring the resistance to Botulinum toxin type A. Nor did they establish a clear and unambiguous correlation between the presence of antibodies and resistance to Botulinum toxin type A. There was thus no evidence or expectation of success that Botulinum toxin type B would work also in the instance sensitization was not due to the presence of neutralizing antibodies.

VII. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 8 filed as main request on 7 July 2003, or in the alternative, on the basis of claims 1 to 7 filed as auxiliary request at the oral proceedings.

Reasons for the Decision

Main request

Claim 1

1. No objections, either by the examining division or by the board, have been raised with regard to Articles 123(2) and 54 EPC.

Article 56 EPC

2. Claim 1 is directed to a second/further therapeutic application of Botulinum toxin type B, said therapeutic application being the treatment of a neuromuscular disorder in a patient who has experienced a loss of clinical response to the administered Botulinum toxin type A.

Closest prior art and problem to be solved

3. The appellant argues that document (D2) represents the closest prior art, as this document is concerned with solving the same problem stated in present claim 1 of treating patients who experienced a loss of clinical response upon previous treatment with Botulinum toxin type A. However, in the appellant's view, the solution adopted in document (D2), namely switching to Botulinum toxin type F, achieves poor results, *inter alia* because of the short duration of action despite the massive doses of Botulinum toxin type F (see document (D2), page 349, Table 1, under "Total dose" and "Time to full return of symptoms"). In the appellant's opinion, it is the **improved** and non obvious treatment of the above patients with Botulinum toxin type B according to

present claim 1 which overcomes the drawbacks of the use disclosed by document (D2).

4. However, the board observes that the only passage in the present application relating to a treatment with Botulinum toxin type B is Example 1 (see page 5, lines 31-40), according to which a patient suffering from tardive dyskinesia experiences a loss of clinical response upon continued administration of Botulinum toxin type A. Example 1 concludes: "Thereafter, an effective amount of botulinum toxin type B is injected and the symptoms of tardive dyskinesia continue to be markedly reduced".

5. It cannot be derived from this passage that the use according to present claim 1 overcomes the problem of short duration of action affecting the use of Botulinum toxin type F in patients resistant to Botulinum toxin type A. Moreover, the "total patient doses" from 80 U to 460 U used in Example 1 (see page 5, line 18) are comparable to those referred to in document (D2) (see Table 1, under "Total dose"). In conclusion, there is no evidence before the board that the treatment with Botulinum toxin type B according to present claim 1 represents an improved treatment over the use disclosed by document (D2) and this appellant's line of argument thus fails.

6. The board rather views document (D5) as prior art closer to the claimed subject-matter than document (D2). This is because the former document deals with Botulinum toxin types A and B rather than types A and F (document (D2)), while also addressing the problem of loss of clinical response upon treatment with Botulinum

toxin type A (see the paragraph bridging page 182 and 183). With a view to solving this problem, histochemical studies are performed on rabbits with Botulinum toxin type B.

7. For the purpose of assessing the inventive step, it thus has to be examined whether or not the claimed therapeutic application "in a patient" (see claim 1) follows in an obvious manner from this prior art relating to an animal model.

8. It is a well-established and accepted principle that a medical application of a substance can be made plausible to a skilled person by a preliminary pharmacological effect observed either in vitro or on animal models. Yet this is not a general or absolute rule since experimentation in animals may not be indicative of any therapeutic effectiveness in human patients in the case only a poor animal model, if any, for a given disease actually exists.

9. Turning to the present situation, the appellant argues that the latter of the two cases above applies, as in vitro histological experiments with tissues excised from rabbits are not predictive of how Botulinum toxin type B would behave in humans in vivo. However, in the board's judgement, the idea behind the experiments performed according to document (D5) goes beyond that of a mere in vitro test. This is because these investigations depart from the already known **clinical** use of Botulinum toxin type A for treating neurological disorders (see page 182, l-h column, first paragraph) **and** the known pharmacological effect, which translates into a particular histological pattern upon staining

the muscles involved in said clinical use. The result of that study is that Botulinum toxin type B produces on the rabbit's muscles the same histological pattern as does Botulinum toxin type A upon muscles from patients affected by neurological disorders (see page 189, r-h column, lines 4-22). It is thus not surprising that the authors of document (D5) (see ibidem, lines 23-29) are confident that the pharmacological effect (a regional three-month long chemical denervation at the neuromuscular junction) underlying the above histological pattern "useful in the A toxin **will be noted** with the application of B toxin" (see ibidem, lines 23-29; emphasis by the board). In conclusion, document (D5) encourages the skilled person to turn to Botulinum toxin type B for the claimed use. For this reason, the subject-matter of claim 1 is not inventive and the main request is refused.

10. Further arguments maintained by the appellant, namely that there are significant differences in the activities and structures between the various Botulinum toxin serotypes (see Annexes (A), (C) and (F)), cannot convince the board either, because despite these differences, a prerequisite for the clinical application of any botulinal toxin was its capacity of achieving regional and reversible denervation (see document (D5), page 188, r-h column, lines 22-27) and the skilled person was taught by document (D5) that Botulinum toxin type B achieved these effects.

Moreover, the fact that the description of the present application is concerned with Botulinum toxin type C (Example 1(a)), D (Example 1(b)), E (Example 1(c)), and

F (Example 1(d)) for treating type A-resistant patients or Botulinum toxin type E for treating a type B-resistant patient (Example 2) does not assist the appellant on this line of argument.

Finally, Annexes (A), (C) and (F) provided by the applicant to support his case are post-published. Therefore, they cannot be useful for establishing what the skilled person would have done before the priority date of the application at issue.

11. Relying on Annex (B), the appellant argues that there was evidence that antibodies generated against Botulinum toxin type A could cross-react against Botulinum toxin type B, thereby questioning the clinical efficacy of Botulinum toxin type B. However, post-published Annex (B) does not reflect the skilled person's knowledge before the priority date of the present application.

Before that date, the main cause for sensitization to Botulinum toxin type A was believed to reside in the neutralizing antibodies that arose against Botulinum toxin type A upon repeated injection (see document (D5), page 182, r-h column, line 14 to page 183, l-h column, line 10) and no other mechanism had been proposed. But the skilled person was confident that these neutralizing antibodies against the "active site" of Botulinum toxin type A could not render Botulinum toxin type B (completely) ineffective because these molecules were immunologically distinct (see ibidem, page 189, l-h column, last four lines). Therefore, despite document (D5) not describing any assay for quantifying the resistance to Botulinum toxin type A, the skilled

person would have expected that Botulinum toxin type B would also work in the presence of neutralizing antibodies against Botulinum toxin type A.

Auxiliary request

12. Claim 1 of this request is identical to claim 1 of the main request. Therefore, the conclusion arrived at under point 9 supra also applies to the auxiliary request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

C. Eickhoff U. M. Kinkeldey