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Datasheet for the decision of 10 March 2015

Case Number: T 1972/10 - 3.3.04

Application Number: 03015590.7

Publication Number: 1366771

IPC: A61K38/48

Language of the proceedings: EN

Title of invention:
Use of the neurotoxic component of Botulinum toxin for treating muscle spasm

Patent Proprietor:
Allergan Inc.
Merz Pharma GmbH & Co. KGaA

Opponent:
Solstice Neurosciences, Inc. (opposition withdrawn)

Headword:
Botulinum toxin/ALLERGAN

Relevant legal provisions:
EPC Art. 76(1)

Keyword:
Divisional application - added subject-matter (yes)

Decisions cited:
G 0001/06

Catchword:

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Case Number: T 1972/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 March 2015

Appellant: (Patent Proprietor 1)	Allergan, Inc. 2525 Dupont Drive Irvine, CA 92612 (US)
Appellant: (Patent Proprietor 2)	Merz Pharma GmbH & Co. KGaA Eckenheimer Landstrasse 100 60318 Frankfurt Main (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 19 July 2010 revoking European patent No. 1366771 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
K. Garnett

Summary of Facts and Submissions

I. An appeal was filed by the patent proprietors (appellants) against the decision of the opposition division to revoke European patent No. 1 366 771. The patent is entitled "*Use of the neurotoxic component of Botulinum toxin for treating muscle spasm*".

II. The revoked patent was filed as European patent application No. 03 015 590 which was a divisional application of parent European application No. 99 203 920, published as EP 1 005 867, which itself was a divisional of European application No. 95 906 674, published as international application No. WO 95/17904. In due course an opposition was filed by Solstice Eurosciences, Inc.

III. In the written reasons for decision under appeal dated 19 July 2010, the subject-matter of claim 1 of the patent was found not to satisfy the requirements of Article 76(1) EPC because it was not clearly and unambiguously derivable from the disclosure of the parent and grandparent applications with respect to the feature of claim 1 "*the neurotoxic component of a Botulinum toxin*". In particular, both the parent and grandparent application did not directly and unambiguously disclose the claimed use of the neurotoxic component of a Botulinum toxin **isolated** from neurotoxin associated proteins (NAPs) (emphasis added by the board).

IV. With a letter dated 17 November 2010, the opposition was withdrawn.

V. Following a communication of the board setting out its preliminary appreciation of the substantive and legal

matters concerning the appeal, the appellant submitted a new main request and five auxiliary requests with a letter dated 10 February 2015.

VI. Claim 1 of this main request is identical to claim 1 as granted and reads:

"1. Use of the neurotoxic component of a Botulinum toxin for the manufacture of a medicament for the treatment of a spastic muscle by means of intramuscular injection, whereby medicaments for the administration to a patient of a Botulinum toxin of a selected serotype until the patient develops neutralizing antibodies, and thereafter administration to the patient of another Botulinum toxin of a different serotype, are excluded".

VII. Oral proceedings before the board took place on 10 March 2015.

VIII. The requests of the appellants at the oral proceedings were that the decision under appeal be set aside and the patent be maintained on the basis of the main request, alternatively on the basis of one of the first to fifth auxiliary requests, all as filed with their letter dated 10 February 2015, alternatively that the case be remitted to the opposition division for further prosecution on the basis of one of these requests. At the end of the oral proceedings the chairwoman announced the decision of the board.

IX. The following documents are mentioned in this decision:

D1: WO 95/17904, published 6 July 1995, filed on 16 December 1994 and claiming a priority dated 29 December 1993 (the grandparent application).

D2: EP-A-1 005 867, published 7 June 2000 (the parent application).

D5: Moyer, Elizabeth, and P. E. Setler. "Botulinum toxin type B: Experimental and Clinical Experience"; In: "Therapy with Botulinum Toxin", edited by Jankovic J. and Hallet M., February 1994, 71-78.

D16: Declaration of Dr. Mitchell Brin dated 10 September 2010.

D17: Declaration of Dr. Leonard Smith dated 10 September 2010.

X. The arguments of the appellants can be summarised as follows:

All requests

Article 76(1) EPC

The term "*Botulinum toxin*" would have been understood by the skilled person at the priority date to refer to the isolated neurotoxic component of Botulinum toxin, as well as to the neurotoxic component in complex with the neurotoxin associated proteins (NAPs). This was *inter alia* reflected in the description of the grandparent application, document D1, page 3, first two full paragraphs. Here it was disclosed that the neurotoxic component of Botulinum toxin had a molecular weight of 150 kD and consisted of a long 100 kD chain and short 50 kD chain, these chains being linked via a disulphide bridge. It was further known that certain serotypes of Botulinum toxin, e.g. type E, may exist in the form of a single chain un-nicked protein, as

opposed to a dichain, the single chain form being less active but which may be converted to the corresponding dichain by nicking with a protease, e. g., trypsin. It was explicitly stated in document D1 that both the single and the dichain were useful in the method of the present invention. This last sentence made no mention of the presence of any NAPs and would have led the skilled person, who was already aware that the term Botulinum toxin could mean the neurotoxic component alone, to conclude that both the single and dichain forms of the neurotoxic component in isolation from NAPs were useful in the method of the present invention, i.e. in the claimed use for the treatment of spastic muscle.

Furthermore, document D5, published in 1994, reflected how the skilled person at the priority date would have interpreted the expression Botulinum toxin. The first paragraph on page 72, headed "*Structure of the Botulinum Toxin Type B. Toxin-Nontoxin Protein Complex*" illustrated that the term Botulinum toxin was used to mean both neurotoxic component complexed with NAPs (i.e. L and M complexes) and the neurotoxic component on its own, i.e. the S or small form. It was telling that the S form was also referred to as the pure toxin protein. The expert declarations of documents D16 and D17 confirmed this interpretation.

It followed that the subject-matter of claim 1 of all requests was fully disclosed in document D1 and therefore met the requirements of Article 76(1) EPC.

Reasons for the Decision

1. The appeal is admissible.

Main Request

Article 76(1) EPC - added subject-matter

2. Article 76(1) EPC states that "*a European divisional application [...] may be filed only in respect of subject-matter which does not extend beyond the content of the earlier application as filed*". According to established case law of the boards of appeal, it is a requirement that the subject-matter of a divisional application must be directly and unambiguously derivable from the earlier application as filed. In the case of a sequence of divisionals consisting of a root (originating) application followed by divisional applications, each divided from its predecessor, anything disclosed in a divisional application must be directly and unambiguously derivable from what is disclosed in each of the preceding applications as filed (G 1/06, OJ EPO 2008, 307, headnote).

3. The subject-matter of claim 1, which is drafted in the Swiss-type format, is the medical use of the neurotoxic component of Botulinum toxin, where the use is the treatment of a spastic muscle by intramuscular injection.

4. As it is uncontested that claim 1 includes, at least as an embodiment, the use of the neurotoxic component of Botulinum toxin isolated from neurotoxin associated proteins, the question to be answered by the board with respect to the requirements of Article 76(1) EPC is

therefore whether the skilled person at the priority date would have regarded this subject-matter as directly and unambiguously derivable from the disclosure of the grandparent application, document D1.

5. To answer the above question it is first to be established how the skilled person, at the priority date, would have interpreted the expression "*Botulinum toxin*", taking into account the common general knowledge at that date. In particular is to be decided whether the common understanding of a skilled person at the time was that a reference to "*Botulinum toxin*" inherently included a reference to the neurotoxic component on its own, stripped of other associated proteins.

6. The description of the grandparent application (document D1), being essentially identical to that of the patent in suit, gives a good picture of the relevant knowledge of the skilled person at the priority date, in particular in the section "*Background of the Invention*" (page 1, line 17, to page 3, line 19). Furthermore, the content of document D5, published in February 1994, very shortly after the priority date, namely 28 December 1993, may also be considered as reflecting the state of the art at and before that date.

7. In document D5 (page 72, 1st paragraph) it is disclosed that "*Botulinum toxin*" consists of a complex of proteins including nontoxin proteins and a neurotoxin. The latter was commonly referred to as the "*neurotoxic component of Botulinum toxin*" (see document D1 page 3, lines 5-14). Indeed, the term "*component*" already implies that the neurotoxin is just one constituent of a larger whole. Document D1 in its presentation of the

background art defines the term "*Botulinum toxin*" as being "*a generic term embracing the family of toxins produced by the anaerobic bacterium Clostridium botulinum [of which] seven immunologically distinct neurotoxins have been identified*". "*Botulinum toxin*" is also used to refer to the products sold commercially for clinical use under the trade names "*DYSPORT*" and "*BOTOX*" (see document D1, page 4, lines 14 to 19), these being Botulinum toxin type A and being formulated in the form of the neurotoxic component in complex with nontoxin proteins which were also known as neurotoxin associated proteins (NAPs) (see document D5, page 72, paragraph 1).

8. Document D5 was referred to by the appellant as demonstrating that the expression "*Botulinum toxin*" was used in the art to mean both the complexed and pure form of the neurotoxin.

9. As is evident from the title, the document is a review of the experimental and clinical experience with Botulinum toxin type B. In the document the expressions "*Botulinum toxin*", the abbreviation "*BTX*" and the term "*toxin*" are all variously used. Careful reading shows that the first two are used when discussing Botulinum toxin as used clinically, i.e. in complex with NAPs (see for instance, page 71, line 1 and page 81, "*Clinical uses of Botulinum toxin type B*"). The term "*toxin*" is used to mean the neurotoxin present in this complex, as can be seen from the following passage from page 72, paragraph 1, cited as an example: "*Formation of an association complex with nontoxin proteins appears to stabilize the activity of the BTXs perhaps by helping maintain a necessary secondary or tertiary structure. It is presumably for this reason that the only commercially available BTX for clinical use, type*

A, is formulated in the form of a ***toxin****-hemagglutinin nontoxin protein complex, rather than as a formulation of pure* ***toxin***". (Emphasis added by the board).

10. It can be seen from the cited passage that the neurotoxic component is referred to as "*toxin*", while this component in isolated form is called "*pure toxin*". There is nothing in the disclosure of document D5 as a whole to suggest that the skilled person at the priority date would have generally considered that references to "*Botulinum toxin*" would have been understood by the skilled person as also referring to "*pure toxin*". Rather, the document read as a whole gives the opposite impression. It is disclosed that there was a general belief that it was beneficial to administer the toxin-hemagglutinin nontoxin protein complex for reasons of stability. Furthermore, given the careful differentiation made between the complexed and isolated neurotoxic component of Botulinum toxin ("*pure toxin*") and given that the only commercially available form of Botulinum toxin was in complex with NAPs, the skilled person would at the priority date have expected that in a situation where the neurotoxic component of Botulinum toxin was to be used stripped of the NAPs, this would have been explicitly mentioned.

11. The board concludes that the appellant's argument that the skilled person at priority date would have considered references to "*Botulinum toxin*" to include a reference to the neurotoxic component of Botulinum toxin on its own is therefore not convincing.

12. The board therefore concludes that the skilled person at the priority date would have understood the expression "*Botulinum toxin*" to mean the neurotoxic component of Botulinum toxin in complex with NAPs, as

present, for example, in the commercially available preparations.

13. It remains to be considered whether the skilled person reading the grandparent application, document D1, in the light of this interpretation of the expression "*Botulinum toxin*", would have been able to directly and unambiguously derive the claimed subject-matter from this earlier application.

14. The only passages of document D1 pertaining to the neurotoxic component of the Botulinum toxin are found on page 3, lines 5 to 24, and are reproduced below:

"*The neurotoxic component of Botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, i.e., by interfering with the exocytosis of acetylcholine, by decreasing the frequency of acetylcholine release, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind to the presynaptic membrane.*

The "short" and "long" chains are linked together by means of a simple disulfide bridge. (It is noted that certain serotypes of Botulinum toxin, e. g., type E, may exist in the form of a single chain un-nicked protein, as opposed to a dichain. The single chain form is less active but may be converted to the corresponding dichain by nicking with a protease, e. g., trypsin. ***Both the single and the dichain are useful in the method of the present invention.****)*" (emphasis added by the board).

15. These passages would have been read in the context of the application as a whole. In the paragraphs preceding the above citation it is explained that "*Botulinum toxins, in particular Botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders*" (page 1, line 20 to page 2, line 22). It is then explained that "*the term Botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium Clostridium Botulinum and, to date, seven immunologically distinct neurotoxins have been identified* [which] *have been given the designations A, B, C, D, E, F and G.*"

16. In the opinion of the board, the skilled person reading the passage of the description referring to the neurotoxic component would have read it in the context of the immediately preceding passages cited above, and would have seen it it as providing information about the structure and function of Botulinum toxin. Thus, the statement that "*Both the single and the dichain are useful in the method of the present invention*" would have been taken at face value, that is to say, that "*Botulinum toxins*" **comprising** the neurotoxic component either in nicked di-chain or unnicked single chain form could be used in the claimed medical use, but not as a disclosure that the neurotoxic component **stripped of NAPs** should be used in the disclosed invention.

17. The board cannot identify any other passage of document D1 that would have led the skilled person to the conclusion that the neurotoxic component **stripped of NAPs** should be used in the disclosed invention. Indeed the expression "*Botulinum toxin*" is used throughout document D1 and nowhere is there an explicit or implicit disclosure of the claimed use where that use is of the neurotoxic component stripped of NAPs. For

example, the section of document D1 concerning the administration of the toxin (page 8, final paragraph to page 9, first paragraph), mentions the commercially available "*Botulinum toxins*", which consist of the neurotoxin in complex with associated proteins (see section 7.). It follows that in this section the term can only mean the complexed form of the toxin.

18. Indeed, document D1 uses the terms "*Botulinum toxin*" and "*neurotoxic component*" carefully. The former is used in the examples while the latter is only mentioned once in the entire document (see the passage at page 3, under the heading "*Background of the Invention*"). This passage is a description of the structure and function of "*Botulinum toxin*".

19. The declarations of documents D16 and D17, made long after the priority date, were provided by the appellant as expert opinions on the disclosure of document D1. In document D16, the author, Dr. Brin, states his opinion that the skilled person reading document D1 would from the passage at page 2, which reads "*Both the single and the dichain are useful in the method of the present invention*", directly and immediately understand that it discloses the use of the isolated neurotoxic component of Botulinum toxin in the medical use claimed (see document D16, at page 3, item 16 (3)). Similarly, in document D17 at item 13, Dr. Smith uses identical language to reach the same opinion as Dr. Brin.

20. However, the board has in point 16 above already explained why it does not share this view. Moreover, the opinions expressed in documents D16 and D17 cannot override the available contemporary evidence nor can they be used to re-interpret the description of

document D1 in a manner other than that which the skilled person at the priority date would have done.

21. In summary, the board concludes that the skilled person reading the passage in document D1 which states that "*Both the single and the dichain are useful in the method of the present invention*" would conclude that "*Botulinum toxin*" from all the various serotypes, including those that produce an un-nicked single chain variant, may be used in the invention but not that the single and di-chain variants of the neurotoxic component of Botulinum toxin in **isolated** from NAPs may be used in the invention.

22. The board therefore concludes that the grandparent application, document D1, does not directly and unambiguously disclose the claimed use of the neurotoxic component of Botulinum toxin isolated from neurotoxin associated proteins.

23. The subject-matter of claim 1 therefore does not meet the requirements of Article 76(1) EPC.

Auxiliary Requests 1 to 5

24. The medical use of the isolated neurotoxic component of Botulinum toxin is an embodiment of the subject-matter of claim 1 of each of these requests. The reasoning concerning the requirements of Article 76(1) EPC concerning claim 1 of the main request set out in points 2 to 23 above therefore applies equally to the subject-matter claim 1 of all auxiliary requests, which therefore do not meet the requirements of Article 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated