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Datasheet for the decision of 1 February 2022

Case Number: T 1639/16 - 3.3.07

Application Number: 10181506.6

Publication Number: 2266599

IPC: A61K38/48, A61K47/36, A61K31/728, A61P21/02, A61P25/06, A61K8/64, A61K9/00, A61K47/02, A61K47/10, A61K47/26, A61K47/32, A61Q19/00, A61Q19/08

Language of the proceedings: EN

Title of invention:
Therapeutic composition with a botulinum neurotoxin

Patent Proprietor:
Merz Pharma GmbH & Co. KGaA

Opponent:
ALLERGAN, INC.

Headword:
Composition with a botulinum neurotoxin / MERZ PHARMA

Relevant legal provisions:
EPC Art. 100(c), 76(1), 100(b), 83, 100(a), 56

Keyword:

Divisional application - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

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Beschwerdekammern

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Case Number: T 1639/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 1 February 2022

Appellant: (Opponent)	ALLERGAN, INC. 2525 Dupont Drive Irvine CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Merz Pharma GmbH & Co. KGaA Eckenheimer Landstrasse 100 60318 Frankfurt (DE)
Representative:	Ricker, Mathias Wallinger Ricker Schlotter Tostmann Patent- und Rechtsanwälte Partnerschaft mbB Zweibrückenstrasse 5-7 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 May 2016 rejecting the opposition filed against European patent No. 2266599 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 266 599 (hereinafter "the patent") was granted on the basis of 17 claims. The patent is based on European patent application EP 10 181 506.6, which was filed as a divisional application of EP 05 765 454, published as WO 2006/020208 (earlier application). The independent claims of the patent as granted read as follows:

"1. A botulinum neurotoxin preparation comprising at least one botulinum neurotoxin selected from *Clostridium botulinum* of types A, B, C1, D, E, F and G, wherein said at least one neurotoxin is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, and a non-proteinaceous stabilizing agent for botulinum neurotoxin which retains the biological activity of the botulinum neurotoxin in an aqueous solution, wherein said stabilizing agent is hyaluronic acid, and wherein said preparation is free from mammalian-derived proteinaceous stabilizing agents selected from albumin and gelatin."

"10. A method for stabilizing at least one botulinum neurotoxin selected from *Clostridium botulinum* of types A, B, C1, D, E, F and G, wherein said at least one neurotoxin is free of the complexing proteins which naturally form complexes with botulinum neurotoxins, comprising intermixing said at least one neurotoxin with a non-proteinaceous stabilizing agent for botulinum neurotoxin in an aqueous solution in an amount effective to retain the biological activity of the neurotoxin, wherein said stabilizing agent is hyaluronic acid and wherein said preparation is free

from mammalian-derived proteinaceous stabilizing agents selected from albumin and gelatin."

"16. A botulinum neurotoxin preparation as defined in any of claims 1 to 4 for use in the treatment of a condition selected from blepharospasm, hemifacial spasms, spasmodic torticollis, spasticities, migraine, low back pain, cervical spine disorders, strabismus, hyperhidrosis, hypersalivation and dystonias."

"17. A method for treating a cosmetic condition selected from wrinkling and pronounced wrinkling comprising administering a botulinum neurotoxin preparation as defined in any of claims 1 to 4."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and its subject-matter extended beyond the content of the earlier application as originally filed.

III. The opposition division took the decision to reject the opposition.

IV. The following documents filed during the opposition proceedings are relevant for the present decision:

D1: WO 2004/060384 A2
D3: US 2003/0118598 A1
D6: WO 00/74703 A2
D8: International Journal of Biological Macromolecules, 22, (1998), 17-22

V. The opposition division decided in particular as follows:

(a) The subject-matter of the granted claims was directly and unambiguously derivable from the original earlier application.

(b) The patent provided one embodiment of how to perform the invention and the skilled person would rely on its common general knowledge to select an appropriate hyaluronic acid. The opponent had furthermore not provided any specific example of a hyaluronic acid not suitable to achieve the claimed stabilizing function. The requirements of sufficiency of disclosure were thus met.

(c) Document D3 was the closest prior art. The difference between the claimed subject-matter and D3 resided in (i) the selection of hyaluronic acid as polysaccharide stabilizer and (ii) the use of botulinum neurotoxin free of complexing proteins. There was no functional interaction between these two features. Partial problems were thus formulated, as follows: (i) provision of an alternative stabilizing agent for a botulinum toxin composition and (ii) provision of a neurotoxin composition which induces the formation of fewer antibodies. None of the cited prior art suggested to use hyaluronic acid as stabilizing agent for botulinum neurotoxin compositions which are free of complexing proteins. The first partial problem was thus solved in a non-obvious manner. Inventive step was consequently acknowledged.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1 to 4 filed therewith. With letter of 22 February 2018, the respondent filed two further auxiliary requests numbered 1a and 3a.

VIII. The following item of evidence was filed by the appellant on 14 June 2017:

D9: 18 first lines of paragraphs "4.1. Introduction" of "Biochemistry of Cryoprotectant by Kenneth B. Storey, Janet M. Storey", 1991

IX. Oral proceedings were held before the Board on 1 February 2022.

X. The appellant requested that the decision under appeal be set aside and that the patent be revoked. It further requested not to admit auxiliary requests 1 to 4 into the appeal procedure, and to admit D9 in the procedure should auxiliary request 4 be admitted.

XI. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained as granted (main request) or that the patent be maintained on the basis of one of the auxiliary requests 1, la, 2, 3, 3a and 4 wherein auxiliary requests 1, 2, 3 and 4 have been filed with the reply to the statement setting out the grounds of appeal on 30 January 2017 and auxiliary requests la and 3a have been filed with letter of 22 February 2018.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of the granted claims extended beyond the content of the original earlier application EP 05 765 454. In particular, in the present wording, in the case of a preparation containing several neurotoxins, only one of them had to be free of complexing proteins, while in the original earlier application all the neurotoxins were uncomplexed. Furthermore, the combination of hyaluronic acid as stabilizing agent together with the absence of albumin and gelatin was not disclosed in the original earlier application.

(b) The subject-matter claimed was not sufficiently disclosed in the patent. In particular, the patent did not teach how to achieve the claimed retention of activity.

(c) The claimed preparations differed from the formulations of the closest prior art D3 in that (i) hyaluronic acid was selected as stabilizing agent and (ii) the formulated botulinum neurotoxin was free of complexing proteins. No particular effect had been demonstrated over the formulations of D3. The objective technical problem resided in the provision of an alternative stabilized botulinum neurotoxin preparation. The two distinguishing features had no synergistic effect, so that their obviousness could be assessed independently of each other. D3 disclosed uncomplexed neurotoxins and the induced reduction of immunogenicity was known from D3 and D6. This feature did thus not involve an inventive step. D3 further generally taught the use of polysaccharides

as stabilizing agent and D1 revealed the lack of incompatibility between hyaluronic acid and botulinum neurotoxins. The skilled person would therefore have considered using hyaluronic acid, which constituted a subgroup of polysaccharides, as an obvious solution. As a result, the subject-matter of the granted claims was not inventive.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The requirements of Articles 76(1) and 123(2) EPC were met. In particular, the rewording performed in the granted claims did not extend beyond the content of the original earlier application EP 05 765 454 and the introduced features were disclosed in the description of the original earlier application.

(b) The patent as a whole provided sufficient guidance for the skilled person to perform the claimed invention, including with regard to the functional definition of the stabilizing agent.

(c) The claimed preparations differed from the formulations of the closest prior art D3 in that (i) hyaluronic acid was selected as stabilizing agent and (ii) the formulated botulinum neurotoxin was free of complexing proteins. The feature (i) enabled to stabilise the neurotoxin while avoiding pathogen transmission and the feature (ii) reduced the immunogenicity of the formulation. Uncomplexed neurotoxins were however known as less stable than complexed ones. The distinguishing features were therefore interrelated, so that the present subject-matter was a combination invention. The

objective technical problem resided in the provision of an alternative stabilized botulinum neurotoxin preparation avoiding transmission of pathogens and having low immunogenicity. None of the cited prior art documents suggested to use hyaluronic acid as stabilizing agent of relatively less stable uncomplexed neurotoxin to solve the problem posed. The subject-matter of the granted claims was therefore inventive.

Reasons for the Decision

Main request - patent as granted

1. Amendments

1.1 Granted claim 1 corresponds to original claim 15 of the earlier application (EP 05 765 454) wherein:

(a) the definition of the neurotoxins was amended by replacing "a botulinum neurotoxin [...] or a mixture of two or more botulinum neurotoxins, wherein the neurotoxin or mixture of neurotoxins is free of" by "at least one botulinum neurotoxin [...] wherein said at least one neurotoxin is free of",

(b) the stabilizing agent was limited to hyaluronic acid, and

(c) the preparation was defined as being "free of mammalian-derived proteinaceous stabilizing agents selected from albumin and gelatin".

1.1.1 Regarding the amendment (a), both parties agreed that, according to original claim 15 of the earlier application, all the botulinum neurotoxins as previously defined and contained in the preparation (independently of their number) had to be free of complexing proteins. The Board sees no reason to deviate from this interpretation.

However, the parties disagreed as to the interpretation of the corresponding amended feature in present claim 1. The appellant argued that present claim 1 merely required that at least one neurotoxin had to be free of the listed proteins. This meant that in the case of a preparation containing more than one neurotoxin, one had to be free of complexing proteins but the others might be in complexed form. This embodiment extended beyond the content of the original application.

The Board notes that the expression "said at least one" in granted claim 1, when further defining the neurotoxin as being free of the listed complexing proteins, is decisive. The term "said" provides a direct and unambiguous reference to the "at least one neurotoxin" previously defined. The Board considers that due to this reference, the limitation to neurotoxin being free of complexing proteins applies to the previously defined neurotoxin(s) in general *i.e.* as a group of components independently of their amount. It follows from this interpretation that granted claim 1 also provides that all the botulinum neurotoxins (independently of their number), as previously defined and contained in the preparation, must be free of complexing proteins. Accordingly, this rewording does not lead to any extension of the subject-matter of granted claim 1 beyond the one claimed in the original earlier application.

1.1.2 Regarding the amendments (b) and (c), it was undisputed that:

- hyaluronic acid is disclosed as part of a list of preferred non-proteinaceous stabilizing agents in paragraph [0034] of the original earlier application (amendment (b)), and

- the absence of albumin and gelatin is disclosed in paragraphs [0037]-[0038] of the original earlier application (amendment (c)).

The appellant argued that these two features were not originally disclosed in combination in the earlier application. Present claim 1 was the result of a two fold selection from two lists, namely selection of:
- hyaluronic acid from paragraph [0034], and
- the absence of albumin and gelatin, indeed disclosed in paragraphs [0037]-[0038], which however had themselves to be selected from the list of preferred embodiments constituted by paragraphs [0019]-[0040].

The original paragraphs [0019]-[0040] of the earlier application are separated paragraphs defining individual preferred embodiments of the botulinum neurotoxin preparation. Said paragraphs relate to various features defining different chemical and physical properties of the claimed preparation (e.g. the pH, the presence of a cryoprotectant, the possibility of being freeze-dried) or its different uses, and cannot thus be considered to constitute one long list of alternative embodiments as suggested by the appellant. Original paragraph [0038] defines a botulinum preparation wherein the preparation is free of the mammalian derived proteinaceous stabilizing

agents, albumin and gelatin. This preferred embodiment corresponds to the feature introduced in present claim 1 (amendment (c)). This feature does therefore not require any selection from a list of preferred embodiments but rather corresponds directly to a preferred embodiment of the original earlier application. Consequently, merely a one fold selection among the list of preferred non-proteinaceous stabilizers of paragraph [0034] of the original earlier application is required to arrive separately at the features introduced in present claim 1.

Furthermore, according to the original earlier application, one main purpose of the invention is the replacement of mammalian-derived proteinaceous stabilizers by non-proteinaceous stabilizers, so as to avoid potential pathogen transmission (see, for example, paragraphs [0003], [0015], [0074] and the examples of the original earlier application). The combination of the presence of a preferred non-proteinaceous stabilizer (based upon original [0034]) and of the absence of the mammalian derived proteinaceous stabilizers, gelatin and albumin (original paragraph [0038]), is therefore directly and unambiguously derivable from the original parent application.

1.1.3 The same reasoning applies *mutatis mutandis* to the independent claims 10, 16 and 17 as granted.

1.1.4 The appellant also generally objected that the dependent claims further added new subject-matter, as they defined combinations with additional features.

In the Board's view, the subject-matter of the dependent claims correspond to individually disclosed

preferred embodiments (see claims and/or description) of the original earlier application. The board considers that the skilled person would have directly and unambiguously derived from the original earlier application that said preferred embodiments referring to different individual components of the product or method claims could be combined with each other and with the features of the respective independent claims.

Concerning claim 8, addressed more particularly by the appellant, the Board observes that paragraph [0057] of the original earlier application specifically discloses the three polyalcohols of present claim 8 as preferred cryoprotectants in the context of a composition comprising a botulinum neurotoxin for a specific medical use. The Board considers that the skilled person would have understood that said preferred cryoprotectants apply also to the composition *per se*.

1.1.5 Therefore, the presently claimed subject-matter does not extend beyond the content of the earlier application as originally filed (Article 76(1) EPC).

1.2 The appellant did not raise any objection regarding amendments *versus* the original divisional application. The Board is satisfied that the presently claimed subject-matter does not extend beyond the content of the divisional application as originally filed (Article 123(2) EPC).

1.3 Accordingly, the ground of opposition under Article 100(c) EPC does not prejudice the maintenance of the granted patent.

2. Sufficiency of disclosure

2.1 The granted claims relate to a botulinum neurotoxin(s) preparation wherein the neurotoxin(s) is (are) free of the naturally complexing proteins and the preparation is free of the proteinaceous stabilizing agents albumin and gelatin. The preparation contains instead a non-proteinaceous stabilizer defined in structural (hyaluronic acid) as well as functional ("retains the biological activity of the botulinum neurotoxin in an aqueous solution") terms.

2.2 The appellant disputed that the patent provided sufficient information concerning:
(i) how the retention of activity was to be determined, and
(ii) which hyaluronic acids fulfilled the claimed function.

2.3 Regarding point (i), the Board observes that the functional definition of the stabilizing agent in granted claim 1 provides a qualitative and not a quantitative definition of the retention of activity.

The skilled person willing to perform the invention would thus turn to common general knowledge and the description of the patent to interpret the terms "retains the biological activity".

As argued by the respondent, the skilled person would know from common general knowledge, that a loss of activity of botulinum neurotoxin occurs over time. The literal interpretation made by the appellant (*i.e.* maintenance of the activity at its initial level) would therefore not be considered by the skilled person as a reasonable interpretation. The skilled person reading

the description of the patent would then find in paragraphs [0046] and [0061] the indication that a loss of toxicity of up to 80% (compared to initial toxicity) may occur over time while still considering the activity as stabilised, *i.e.* the retention of activity as achieved. This is further in line with the results provided in the examples which show that similar levels of toxicity are achieved as in the presence of the common mammalian-derived proteinaceous stabilizer Human Serum Albumin (HSA), despite some loss of toxicity over time (see in particular example 4). In the Board's view, the skilled person would thus derive from the patent as a whole that the functional definition used in the claims is to be interpreted as meaning that the level of toxicity may decrease but must be maintained to at least 20% of its initial level.

2.4 In this context the appellant argued during oral proceedings that the above mentioned paragraphs [0046] and [0061] did not substantiate this interpretation. Paragraph [0046] provided a definition of the term "stabilizing" not "retain". The first sentence of paragraph [0061] confirmed that the activity had to be maintained substantially at its initial level and the second sentence referred to reconstituted solution (while the claims referred to an aqueous solution).

This argument is not convincing. The term "retains" is used in the granted claims to functionally define the stabilizing agent. The skilled person would thus have understood that the definition of the term "stabilizing" provided in paragraph [0046] applied to the claimed stabilizing agent. Regarding paragraph [0061], the Board observes that it does not belong to the section "Definitions" of the patent but to the section "Description". The first sentence of this

paragraph describes therefore merely one embodiment of the invention, in which substantially no potency loss occurs. This does not mean that the invention is limited thereto. Regarding the second sentence, in the Board's view, the broad reference to an aqueous solution in the granted claims do not exclude the option that it is a reconstituted solution.

2.5 For the reasons detailed under point 2.3 above, the functional feature to be achieved by the stabilizer can be evaluated based on a comparison of the initial level of toxicity and the level after some time. It has not been disputed that methods for the measurement of botulinum neurotoxin toxicity are available to the person skilled in the art. Moreover the patent provides in paragraph [0061] indications regarding time periods and storing conditions. It follows that the absence of the mention of a specific method in the patent would not prevent the skilled person from performing said comparative evaluation using any known method and thus determine whether a given hyaluronic acid would indeed fulfill the claimed functional feature or not.

2.6 Regarding point (ii), the Board observes that the patent does indeed not specify which specific hyaluronic acid to use, so that the skilled person would need to refer to common general knowledge and commonly known hyaluronic acids. The appellant did however not provide any evidence in support of the fact that any specific hyaluronic acid would not achieve the claimed function.

The argument of the appellant that the examples of the patent in suit themselves showed that the claimed functional definition was not fulfilled is not convincing. According to the interpretation of said

functional feature as made under point 2.3, the hyaluronic acid used in the examples achieve the claimed retention of activity (see example 4).

Furthermore,the patent provides guidance regarding the amount of hyaluronic acid to be used (see paragraph [0062]).

2.7 The appellant also raised an objection regarding the lack of achievement of the stabilizing effect over the whole scope of the claims, in view of the examples of the patent themselves. As stated above, the Board considers that the examples relate to hyaluronic acid actually achieving the claimed function as revealed by example 4. Moreover the Board notes that the retention of activity is a functional definition of the stabilizing agent (namely hyaluronic acid) to be used in the claimed preparation and methods. The Board does not share the approach of the appellant consisting in considering said feature as a parameter to be achieved by any final preparation. It follows that the fact that further features, such as pH and lyophilization conditions, may impact the stability (and thus toxicity) of the final preparation is not relevant with regards to the functional definition of the stabilizer *per se*. This consideration applies in particular to the complete loss of activity observed for some samples in example 5 by the sixth day. It is immediately apparent that the loss of activity is due to the pH of the solutions, since the same loss is observed when using human serum albumin instead of hyaluronic acid. In any case the Board observes that the patent in suit provides guidance on how to select these further features (preferred pH and addition of cryoprotectants; see paragraphs [56] to [58] and [62] to [64]).

2.8 As a result, in the absence of serious doubts substantiated by verifiab1e facts, that the claimed invention cannot be performed, the ground of opposition under Article 100(b) EPC in combination with Article 83 EPC does not prejudice the maintenance of the granted patent.

3. Inventive step

3.1 Closest prior art

3.1.1 The patent in suit relates to a botulinum neurotoxin preparation comprising:
- at least one botulinum neurotoxin selected from *Clostridiuin botulinum* of types A, B, Cl, D, E, F and wherein said neurotoxin(s) is free of complexing protein, and
- a non-proteinaceous stabilizing agent being hyaluronic acid,
wherein the preparation is free of albumin and gelatin.
A method of stabilizing said botulinum neurotoxin(s) using hyaluronic acid in the absence of albumin and gelatin as well as medical and cosmetic uses of said preparation are also claimed.

According to the patent, the invention aims at providing a stable botulinum neurotoxin preparation having low immunogenicity and reduced risk of pathogen transmission.

3.1.2 In agreement with both parties, the Board considers D3 to represent the closest prior art.

D3 relates to pharmaceutical compositions comprising a botulinum neurotoxin and a stabilizer for use in the treatment of neuromuscular disorders. Low

immunogenicity is a further purpose of D3 (see for example paragraphs [0094] or [0178]) . According to claims 1-2 the botulinum neurotoxin can be either in complexed or pure form, however the preferred embodiments and specific examples are directed to complexed neurotoxins. D3 mainly concerns the finding of a replacement stabilizer to avoid mammalian-derived proteinaceous stabilizers due to the associated risk of pathogen transmission (see for example paragraphs[0042] or [0089]). In one embodiment, preferred stabilizers are thus recombinantly made stabilizers including albumin, gelatin and collagen (see claim 4 and paragraphs [0093] and [0119]). In another embodiment, D3 discusses the use of a polysaccharide, in particular hydroxyethyl starch, to stabilise the neurotoxin (see inter alia paragraphs [0124] to [0130], [0134], [0175] to [0177] and [0180]).

3.2 Distinguishing features and

It was undisputed that the claimed subject-matter differs from the one of D3 in:
(i) the specific choice of hyaluronic acid as non-proteinaceous stabilizing agent and
(ii) the limitation to pure (*i.e.* non-complexed) botulinum neurotoxin(s).

3.3 Technical effects and objective technical problem

3.3.1 According to the patent, the distinguishing feature (i) results in an efficient stabilization of the neurotoxin while reducing the risk of pathogen transmission (see *e.g.* paragraphs [0009], [0062] and examples). The distinguishing feature (ii) reduces the immunogenicity of the preparation (see paragraph [0007]). The same technical effects are however also reported in D3 (see

above 3.1.2). No particular effect *versus* the closest prior art D3 has been substantiated for any of the distinguishing features (i)-(ii).

3.3.2 It follows that, starting from D3, the objective technical problem resides in the provision of an alternative stabilized botulinum neurotoxin preparation for use in cosmetic or medical treatments with low risk of transmission of pathogens and low immunogenicity.

3.3.3 During oral proceedings, the parties adhered to this approach.

3.3.4 The examples of the patent, in particular example 4, render credible the resolution of this problem by the claimed preparations.

3.4 Obviousness of the solution

3.4.1 The main point of dispute concerned the obviousness of the solution offered by the patent. In particular, the parties disagreed on the existence of a functional interrelation between the features (i) and (ii) and its impact on the choice of these features.

3.4.2 The Board notes that the use of neurotoxins free of complexing proteins and the associated reduction of immunogenicity are generally taught in D3 (see above 3.1.2) as well as in D6 (see page 3, second full paragraph). The feature (ii) *per se* cannot therefore provide inventiveness to the subject-matter of the granted claims.

3.4.3 The Board considers however that the choice of feature (i) cannot be seen as entirely independent from feature (ii). It was common ground that a botulinum neurotoxin

in a "pure" state has a reduced stability compared to the neurotoxin in a "complexed" state. The description of the patent (see e.g. paragraph [0062] and example 4) indicates that hyaluronic acid stabilizes the neurotoxin. There is therefore a functional reciprocity between the two features. The fact that the effects linked to these two features are not synergistic does not mean that they are not interrelated. Accordingly, the Board does not share the approach of the appellant, which assesses the obviousness of the two features in an entirely independent and separated manner.

3.4.4 The Board observes that D3 generally discloses the use of a polysaccharide as stabilising agent (see *e.g.* paragraph [0124]), but not specifically for uncomplexed neurotoxin. All the examples of D3 concern indeed complexed proteins, and paragraph [0119] refers to the formulation of uncomplexed neurotoxins only in combination with recombinant stabilizers. This paragraph belongs to the section "Summary" of D3 and preparations comprising a polysaccharide as stabilizer are disclosed in this section only later (starting from paragraph [0124]).

Furthermore, even if the term polysaccharide may very generically encompass hyaluronic acid, hyaluronic acid is not disclosed *per se* in D3. D3 concentrates on starch derivatives, in particular hydroxyethyl starch (see paragraph [0124] and examples). Furthermore, D3 describes the choice of the polysaccharide as critical (see paragraph [0195]). The Board is therefore of the opinion that the skilled person would rather be discouraged from using a polysaccharide not individually mentioned in D3. In this context, the appellant argued that the statement regarding criticality was made in the context of the discussion

on the participation of polysaccharides in Maillard reaction. According to the appellant, the skilled person would have been aware that there is no evidence of hyaluronic acid participating in Maillard reaction, as revealed by D8. This reasoning is not convincing, since it implies that the skilled person would already consider specifically hyaluronic acid, and then appreciate that the statement of D3 does not apply to it. There is however no pointer to hyaluronic acid in D3.

The Board therefore considers that D3 does not provide any motivation to use specifically hyaluronic acid, let alone in order to stabilize less stable uncomplexed neurotoxins. Similarly, and contrary to the opinion of the appellant, the skilled person would furthermore not have been motivated to add hyaluronic acid (*i.e.* in addition to hydroxyethyl starch) to the preparations of D3, let alone to modified preparations wherein the neurotoxin would be uncomplexed.

3.4.5 The appellant argued that, since the required level of neurotoxin activity stabilization was low (only 20% retention of the initial activity considered sufficient), the expectation of success would be relatively high. This argument is however not convincing. As detailed above under point 3.4.4, D3 does not provide any hint towards the use of hyaluronic acid to stabilize uncomplexed proteins, so that there cannot be any expectation of success.

3.4.6 The appellant further referred to D1. This document relates to hyaluronate as a further sequestration agent in addition to albumin for botulinum toxin complexes preparations. D1 does not describe hyaluronic acid as stabilizing agent. As brought forward by the appellant,

the skilled person may have learned from D1 that there is no incompatibility between hyaluronic acid and botulinum neurotoxins. D1 cannot however fill the gap regarding the lack of hint towards hyaluronic acid in D3.

3.5 Accordingly, the ground of opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice the maintenance of the granted patent.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated