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Datasheet for the decision of 28 January 2013

Case Number: T 1903/08 - 3.3.02

Application Number: 99964009.7

Publication Number: 1135166

IPC: A61K 47/48

Language of the proceedings: EN

Title of invention:
Hapten-carrier conjugates for treating and preventing nicotine addiction

Patent Proprietor:
Nabi Biopharmaceuticals

Opponent:
Cytos Biotechnology AG

Headword:
Conjugates for nicotine addiction/NABI

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no), subject-matter of all requests obvious in view of combination of two documents of the state of the art"

Decisions cited:
-

Catchword:
-

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Case Number: T 1903/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 28 January 2013

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 1 August 2008 concerning maintenance of European patent No. 1135166 in amended form.**

Composition of the Board:

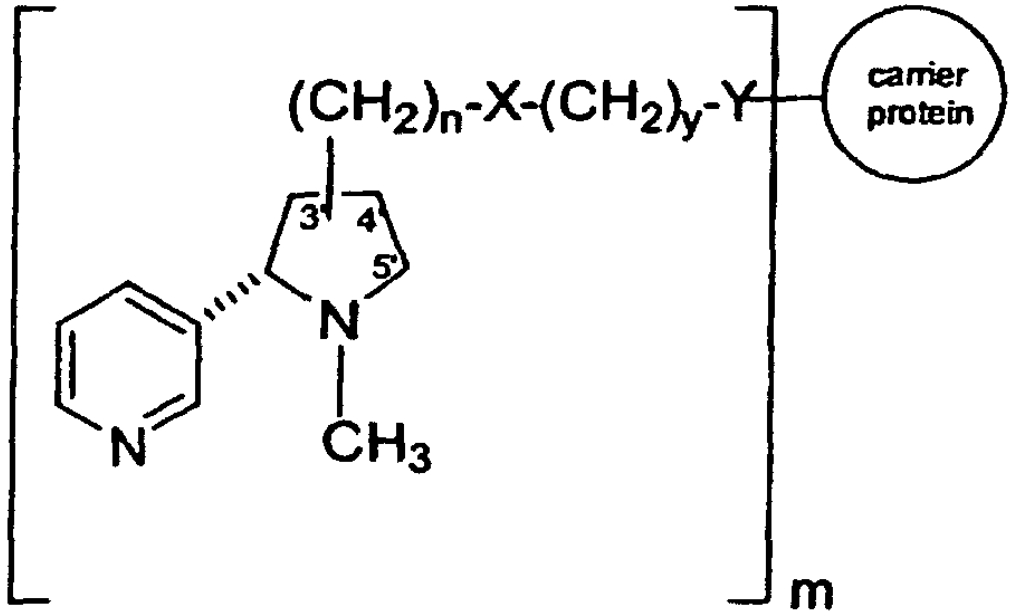
Chairman: U. Oswald
Members: H. Kellner
R. Cramer

Summary of Facts and Submissions

I. European patent No. 1 135 166, based on international application PCT/US1999/028272, published as WO 2000/032239 and having application No. 99 964 009.7 in the EPO, was granted with 28 claims.

Independent claims 1, 7, 10, 13, 14, 15, 18 and 27 as granted read as follows:

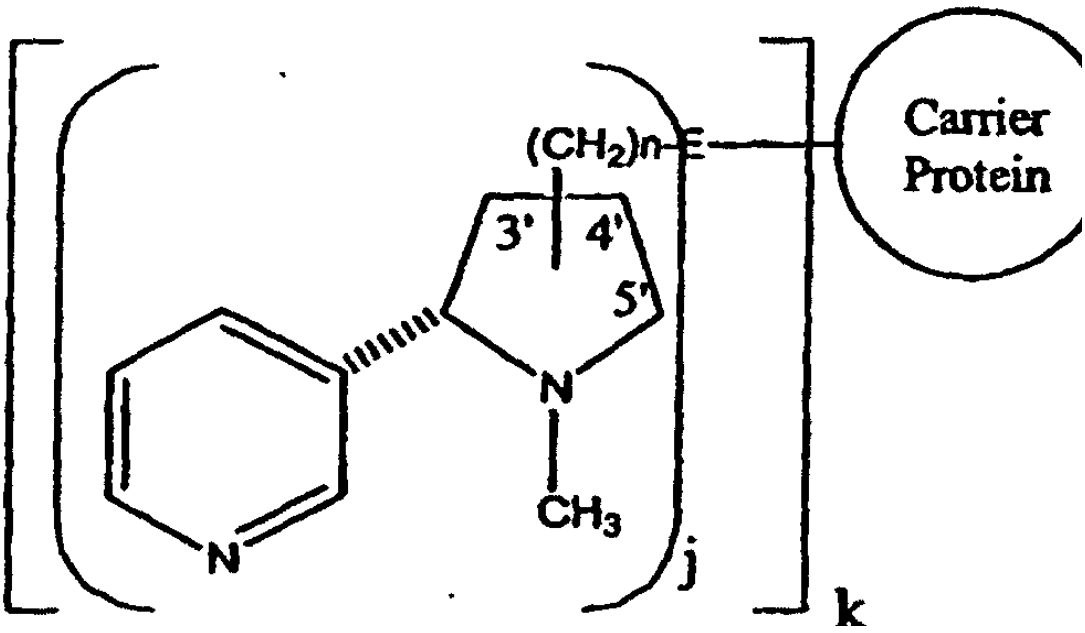
"1. A hapten-carrier conjugate of the following formula:



wherein
m is 1 to 2500,
n is 0 to 12,
y is 1 to 12,
X is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S;
Y is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S,

and the $-(CH_2)_n-X-(CH_2)_y-Y-$ moiety is bonded to the 3', 4' or 5' position of nicotine.

7. A hapten-carrier conjugate of the following formula:



wherein n is 0 to 12, j is 1 to 1000, k is 1 to 20, and E is an amino acid-containing matrix.

10. An antibody produced in response to the hapten-carrier conjugate according to any one of claims 1 to 9.

13. A functional fragment of the antibody of claim 10.

14. A kit for determining the presence of nicotine in a sample, comprising an antibody or a functional fragment thereof according to any one of claims 10 to 13.

15. A process for producing an antibody, comprising immunizing a host mammal with the hapten-carrier conjugate of any one of claims 1 to 9.

18. A vaccine composition comprising at least one hapten-carrier conjugate according to any one of claims 1 to 9.

27. Use of a hapten-carrier conjugate according to any one of claims 1 to 9 or an antibody or a functional fragment thereof according to any one of claims 10 to 13 for the preparation of a medicament for the treatment or prevention of nicotine addiction."

II. Opposition was filed against the granted patent under Article 100(a) EPC, lack of novelty and inventive step, and Article 100(b) EPC, insufficiency of disclosure.

III. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

(1) Langone, J.J. et al., "Radioimmunoassay of nicotine, cotinine, and γ-(3-Pyridyl)-γ-oxo-N-methylbutyramide", Methods in enzymology, volume 84, 1982, 628-640

(4) WO 98/14216 A2

(5) Castro, A. et al., "Nicotine Antibodies: Comparison of Ligand Specificities of Antibodies Produced against Two Nicotine Conjugates", Eur. J. Biochem., volume 104, 1980, 331-340

(6) Castro, A. et al., "Nicotine antibody production: Comparison of two nicotine conjugates in different animal species", Biochemical and Biophysical

Research Communications, volume 67, no. 2, 1975, 583-589

(7) Matsushita, H. et al., "Conjugate of bovine serum albumine with nicotine", Biochemical and Biophysical Research Communications, volume 57, no. 4, 1974, 1006-1010

(8) Bjercke, R.J. et al., "Stereospecific monoclonal antibodies to nicotine and cotinine and their use in enzyme-linked immunosorbent assays", Journal of Immunological Methods, volume 90, 1986, 203-213

(13) Declaration of Ali I. Fattom dated 3 December 2008

(14) 2nd declaration of Ali I. Fattom dated 24 April 2009

IV. The opposition division held that the contested patent as amended according to the single claim of the fifth auxiliary request (relating to the combination of claim 27 with claim 1 as granted, but restricted to a bond in the 3'-position of nicotine) met the requirements of the Convention.

The decision explicitly included a positive ruling on sufficiency of disclosure, valid for all the requests.

However, claims 7 and 10 of the patent as granted and claims 10, 17 and 20 of the first auxiliary request were anticipated by documents (1), (8) and (4).

Claims 4 of the second, third and fourth auxiliary requests contravened Article 123(2) EPC.

V. Both the opponent and the patentee filed appeals against the decision of the opposition division.

VI. With its statement of grounds of appeal, the appellant-patentee submitted six sets of claims as main request and first to fifth auxiliary requests. The main request referred to the patent as granted. The fifth auxiliary request was identical to the request as maintained by the opposition division (the text of its claim 1 is presented in the following as claim 1 of the current fourth auxiliary request being identical in its wording).

In claim 7 of the first auxiliary request the following text is added at the end of claim 7 of the main request:

"and wherein the matrix is poly-L-glutamic acid".

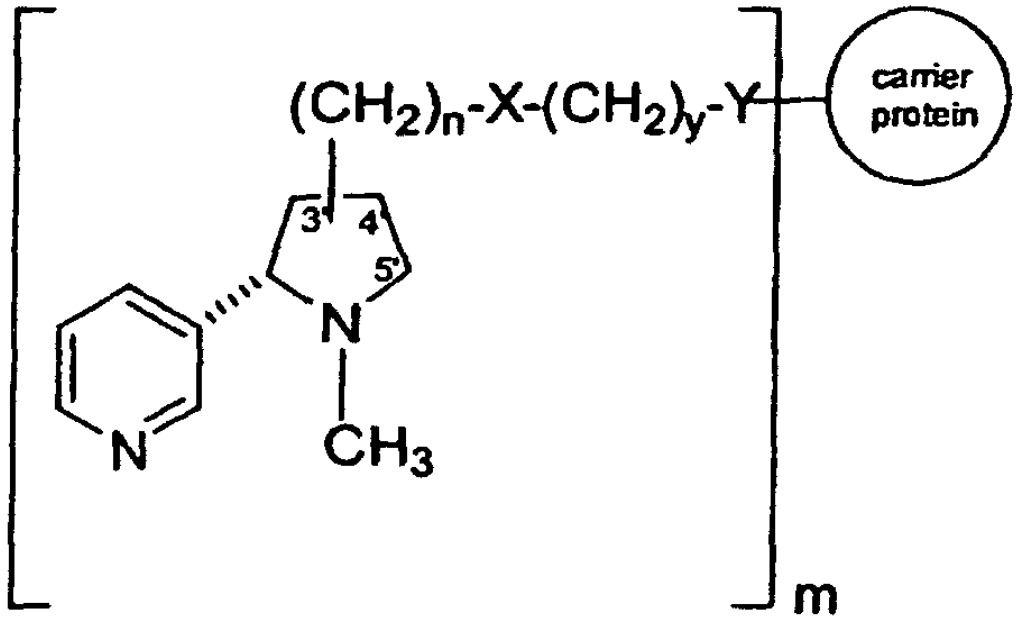
In the second auxiliary request the claims relating to the antibodies and issues with respect to these antibodies in combined claims have been deleted.

The third auxiliary request in principle is restricted to hapten-carrier conjugates relating to claim 1 as granted with a linker bond in the 3'-position and corresponding depending claims. The issue of claim 7 and related subject-matter is deleted.

Claim 1 of the fourth auxiliary request relates to the subject-matter of the third auxiliary request in the second medical use format according to claim 27 as granted. Its wording is (additions with respect to

claim 1 as granted in bold; deleted text in strikethrough):

"Use of a hapten-carrier conjugate for the preparation of a medicament for the treatment or prevention of nicotine addiction wherein the hapten-carrier conjugate has the formula:



wherein
m is 1 to 2500,
n is 0 to 12,
y is 1 to 12,
X is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S;
Y is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S,
and the $-(CH_2)_n-X-(CH_2)_y-Y-$ moiety is bonded to the 3'~~, 4' or 5'~~ position of nicotine."

The wording of the single claim of the fifth auxiliary request as maintained by the opposition division is

identical to the wording of claim 1 of the fourth auxiliary request.

VII. With letter of 20 December 2012, the appellant-patentee informed the board that it would not be attending the oral proceedings.

The appellant-opponent filed a letter, dated 7 January 2013 and indicating that it would not be represented at the oral proceedings and that it withdrew its request for oral proceedings.

VIII. Oral proceedings took place on 28 January 2013 in the absence of the parties.

IX. The appellant-opponent, in its written submissions, raised objections concerning novelty, inventive step and sufficiency of disclosure.

The teaching of the patent in suit could not be carried out by a skilled person because the bond between the linker and the carrier protein in claim 1 of the patent was restricted to N-containing bonds. Despite this, even in the example according to the patent (example 4 together with example 7 and first paragraph on page 7 of the patent) ester-bonds were built in addition and the patent was silent on how to avoid this or on methods of purification.

With respect to inventive step, there was no difference between the conjugates of the patent in suit and those according to document (4) apart from the position where the linker together with the carrier protein was attached to the nicotine molecule: according to

document (4) all positions at the pyridine ring or the 1'-position at the pyrrolidine ring were used; in the patent, linkage at the remaining positions of 3', 4' and 5' pyrrolidine ring was disclosed. However, from document (1) it was already known that a carrier protein-succinyl-link at a hydroxmethylgroup bound to the 3'-position of nicotine also resulted in a hapten-carrier conjugate that allowed to raise antibodies to nicotine. Therefore, no inventive activity was needed to shift the link from one of the positions according to document (4) to the 3'-position, for instance.

X. The appellant (patentee)'s arguments in written form may be summarised as follows:

Closest state of the art was document (4). Document (1) was much older than document (4) and for this reason, and also because it did not deal with a therapeutic use, could not be combined with document (4).

Moreover, the state of the art as a whole, in particular documents (5), (6) and (7) taught away from the invention, since they did not consider modifying the pyrrolidine ring of nicotine.

XI. The appellant-opponent requested in writing that the decision under appeal be set aside and that European patent No. 1 135 166 be revoked.

XII. The appellant-patentee requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or, alternatively, on the basis of one of the first to

fifth auxiliary requests, all filed with the grounds of appeal.

XIII. At the end of the oral proceedings the chairman announced the decision.

Reasons for the Decision

1. The appeals are admissible.

2. Claim 1 of the main request and of the first and second auxiliary requests are identical to claim 1 as granted. Since Article 100(c) EPC is not a ground for opposition in the current case, there is no question of added subject-matter in this respect.

3. *Article 123(2) EPC; third to fifth auxiliary request*

3.1 Claim 1 of the third auxiliary request represents the restriction from a bonding to the 3', 4' or 5' position of nicotine to a bonding to the 3' position, which is as such in line with the provisions of Article 123(2) EPC. Nevertheless, the amendment is further supported by claim 2 of the application as originally filed (represented by WO 2000/032239; corrected version) and by page 9, last two lines together with the formula on top of page 10 and by example 1.

3.2 Claim 1 of the fourth (identical to the single claim of the fifth auxiliary request) is based on original claims 16 and 18 together with original claim 2 in the Swiss-type format of a second medical use claim.

Again, as regards added subject-matter, there is only the restriction from the three possible bonding positions to one of them, with the same additional support as indicated above.

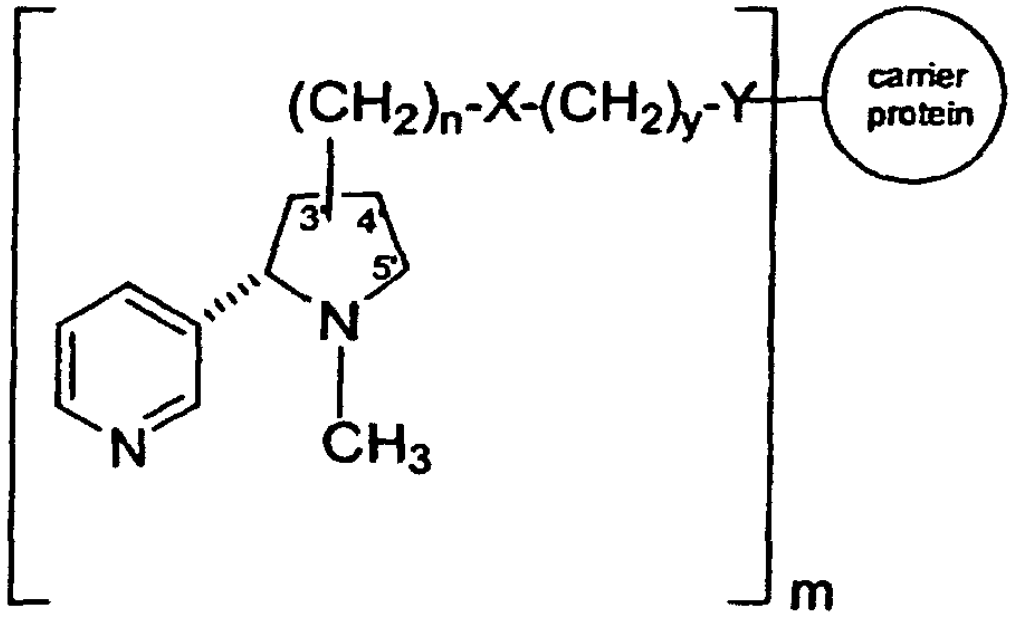
3.3 Therefore, each of the claims 1 of the third to fifth auxiliary requests complies with Article 123(2) EPC.

4. The board is satisfied that the teaching of claim 1 of the main request and of the auxiliary requests can be carried out by the skilled person, because nothing tangible to the contrary has been filed and absolute pureness of a reaction product is not an absolute condition for sufficiency of disclosure (Article 100(b) or Article 83 EPC respectively).

5. *Claim 1 of the main request (identical to claim 1 as granted and identical to claims 1 of the first and second auxiliary requests); Articles 54 and 56 EPC*

5.1 *Novelty*

5.1.1 The subject-matter of this claim 1 relates to the provision of a hapten-carrier conjugate having the formula:



wherein
m is 1 to 2500,
n is 0 to 12,
y is 1 to 12,
X is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S;
Y is selected from the group consisting of NH-CO, CO-NH, CO-NH-NH, NH-NH-CO, NH-CO-NH, CO-NH-NH-CO, and S-S,
and the $-(CH_2)_n-X-(CH_2)_y-Y-$ moiety is bonded to the 3' position of nicotine.

5.1.2 The subject-matter of document (4) relates to the provision of

a hapten-carrier conjugate (see claim 1)

containing nicotine and a carrier protein according to example PS-59 on page 9/14, figure 7b,
being linked in the form of

CJ11 being *YCO(CH$_2$)$_n$COQ* (according to the definition in claim 1 of document (4)) with *Y* is NH, n is 2-8, *Q* is T-cell epitope containing carrier (the alternative OH being irrelevant for a hapten carrier conjugate which must contain a protein carrier)

which means in terms of the patent in suit linked by -(CH$_2$)$_n$-X-(CH$_2$)$_y$-Y- with n being 0, X being NH-CO, y being 2 to 8 (within the range of 1 to 12 in the patent in suit) and

Y being CO-NH bound to protein

(so far the features being identical in the example of document (4) and current claim 1)

or Y being CO-O bound to protein or CO-S bound to protein

and wherein the nicotine is linked at position A (in figure 6b of document (4)) which means the 6-position at the pyridine-ring of the nicotine.

5.1.3 Thus, hapten-carrier conjugates according to document (4), just like the ones claimed in the patent in suit, contain amide-bonds on both ends of the linker-molecule, present nicotine in its natural (S)-(-) formation (see figure 6b of document (4)) and stimulate the production of antibodies that are capable of specifically binding to nicotine which makes them suitable for therapeutic use in treating nicotine abuse (see document (4), claim 17 referring to claim 10 together with page 10, lines 1 to 21).

5.1.4 Nevertheless, the subject-matter of claim 1 of the main request (and of the first and second auxiliary requests) is new with respect to document (4) because of the differing position of the link between nicotine and the protein carrier and, at least according to the literal wording of the claims, the Y-element between the linker and the carrier protein mandatorily containing an N-atom.

In another document, namely document (1), a hapten-carrier conjugate linked at the 3'-position of the nicotine molecule is disclosed. However, the link is accomplished by an ester group at the hydroxymethylated nicotine molecule and not by an N-containing group as defined in claim 1 of these requests (see document (1), figure 2 on page 631, and the paragraph bridging pages 633 and 634 under the headline "Production of antibodies and tracers").

Further, there are no hapten-carrier conjugates disclosed in the other documents of the state of the art on file where the link is in one of the 3', 4' and 5'-positions of the nicotine molecule and where the linker contains N-bearing carboxy-moieties at both its ends (functions X and Y in the structural formula of claims 1 of all requests).

5.2 *Inventive step*

5.2.1 The closest state of the art is document (4). It relates to hapten-carrier conjugates, like the ones of the patent in suit, linked for instance at the 6-position instead of one of the positions 3', 4' and 5' of the nicotine molecule. The hapten-carrier

conjugates according to document (4) contain amide-bonds on both sides of the linker-molecule, present nicotine in its natural (S)-(-) formation and are suitable for therapy in nicotine addiction (see point 5.1.3 of this decision).

5.2.2 There are no examples comparing the nicotine-carrier conjugates of the patent in suit to example PS-59 of document (4); there are not even any examples comparing the nicotine-carrier conjugates of the patent in suit to any of the examples of document (4), even though the appellant-patentee, in its written submissions, was in favour of taking this document as closest prior art. The examples provided contain different linkers and different proteins and give no comparable results.

5.2.3 As a consequence, the problem to be solved is to provide another nicotine-carrier conjugate suitable for therapeutic use in treating nicotine abuse, wherein the hapten-carrier conjugate contains nicotine and a carrier protein connected by a linker consisting of methylene-groups, a carboxy group at the protein binding side and an NH-CO-containing-bond at the nicotine binding side.

5.2.4 The solution according to the patent in suit is to provide a nicotine-carrier conjugate for treatment or prevention of nicotine addiction according to the features of the claim, wherein the $-(CH_2)_n-X-(CH_2)_y-$ Y- linker-moiety is bonded to the 3', 4' or 5'-position of the nicotine molecule and Y in particular is CO-(NH-protein) or S-S-protein.

In view of the experiments set out in the patent in suit, the problem can be considered to be solved.

5.2.5 The skilled person working on medicaments for therapeutic use in the treatment of nicotine abuse based on the production of antibodies specific to nicotine on vaccination of a mammal with a hapten carrier-protein conjugate also knows document (1).

He learns from this document that nicotine-carrier conjugates linked at the 3' position of nicotine and containing a linker $-(CH_2)_n-X-(CH_2)_y-Y-$ with n being 1, X being **O**-CO, y being 2 and Y being CO(NH-protein), CO(O-protein) or CO(S-protein) (as product of reaction of the free acid in the linker and the protein in presence of a particular carbodiimide) induce antibodies in rabbits that bond to nicotine as target molecules (see figure 2 on page 631, and the paragraph bridging pages 633 and 634 under the headline "Production of antibodies and tracers") and therefore basically are suitable as vaccine for treatment or prevention of nicotine addiction (see document (4), page 10).

5.2.6 Thus, it was obvious to try also 3'-derivatised nicotine linked to a carrier protein by a linker as defined in document (4) which results in identifying conjugates which are part of the teaching of the patent in suit.

In particular, according to the common general knowledge of the skilled person, in applying the reaction scheme of document (1), the bond between the linker and the carrier protein - dependent in some way

on the nature of the protein - will result in predominant building of amide bonds to the free amine groups of the protein and additional bonds to hydroxy or thiol groups as far as available, in exactly the same way as in the exemplified conjugate in the patent in suit (see examples 4 and 7 in connection to the first paragraph on page 7 of the patent).

5.2.7 Accordingly, the subject-matter of claim 1 of the main request (identical to claims 1 of the first and second auxiliary requests) is not inventive over a combination of documents (4) and (1).

6. *Claim 1 of the third auxiliary request; Articles 54 and 56 EPC*

The reasons and conclusions from the discussion of the subject-matter of the main request apply *mutatis mutandis because* document (1) explicitly relates to 3'-derivatised nicotine.

7. *Claim 1 of the fourth (identical to the single claim of the fifth) auxiliary request; Articles 54 and 56 EPC*

The subject-matter of this claim relates to the use of a nicotine-carrier conjugate in the manufacture of a medicament for treatment or prevention of nicotine addiction, wherein the hapten-carrier conjugate is the same as in claim 1 of the main request.

There are no differing features between these claims with the exception that the fourth and fifth auxiliary requests relate to the use of the products of claim 1 of the main request in the manufacture of a medicament

for treatment or prevention of nicotine addiction. That is, however, the use for which the products of claim 1 of the main request are suitable and this suitability is the basis of assessment of inventive step with respect to the product claim of the main request.

The products per se are new, but they do not differ from the prior art as regards their suitability for treatment or prevention of nicotine addiction.

Therefore, the conclusion that the provision of the products of claim 1 of the main request is not inventive remains the same when considering the inventive step of the use of these products in the manufacture of a medicament for exactly the same treatment or prevention of nicotine addiction.

8. Under these circumstances the further arguments of the appellant-patentee on file cannot succeed:

In particular, the age of document (1) casts no doubt on the validity of its results. Therefore, even if the author of one or another differing item of prior art writes some years later that in his opinion particular features, for instance binding sites of the carrier protein to the nicotine-hapten, were important to enable the conjugate to induce the production of antibodies that are able to bind nicotine, and does not indicate that the results of document (1) were not correct, then the impact of the results for the discussion remains unchanged.

The skilled person would also combine document (4) and document (1) because he knows that utility for inducing

the production of antibodies that are able to bind nicotine is the precondition for utility in the treatment of nicotine addiction, as is also set out on page 10 of the closest state of the art, document (4).

9. For these reasons, the subject-matter of the main request and the first to fifth auxiliary requests lacks inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald