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Datasheet for the decision of 15 May 2024

Case Number: T 1654/22 - 3.3.07

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Language of the proceedings: EN

Title of invention:

PROCESS FOR THE PREPARATION OF COMPOSITIONS COMPRISING HYALURONIC ACID AND MEPIVACAINE HYDROCHLORIDE

Patent Proprietor:

Teoxane

Opponents:

Vivacy International SA
ALLERGAN, INC.
Laboratoires Vivacy

Headword:

Process for the preparation of compositions comprising hyaluronic acid and mepivacaine hydrochloride / TEOXANE

This datasheet is not part of the Decision
It can be changed at any time and without notice

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0261/19, T 1112/19, T 0574/19

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Case Number: T 1654/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 May 2024

Appellant: (Patent Proprietor)	Teoxane Les Charmilles Rue de Lyon 105 1203 Geneva (CH)
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Appellant: (Opponent 2)	ALLERGAN, INC. 2525 Dupont Drive Irvine CA 92612-1599 (US)
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Appellant: (Opponent 3)	Laboratoires Vivacy 44 rue Paul Valéry 75116 Paris (FR)
Representative:	Tripoz, Inès Cabinet Tripoz Le Pôle Sud 22 rue Seguin 69002 Lyon (FR)
Party as of right: (Opponent 1)	Vivacy International SA Rue du Rhône 13 1204 Geneve (CH)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 May 2022 concerning maintenance of the European Patent No. 3027186 in amended form.**

Composition of the Board:

Chairman D. Boulois
Members: E. Duval
S. Ruhwinkel

Summary of Facts and Submissions

I. The appeals were filed by the patent proprietor (appellant - proprietor), opponent 2 (appellant - opponent 2) and opponent 3 (appellant - opponent 3) against the interlocutory decision of the opposition division finding that, on the basis of auxiliary request 9 filed during the oral proceedings on 14 April 2022, the patent met the requirements of the EPC.

The decision was based on the patent as granted as the main request, on auxiliary requests 1-7 filed on 23 October 2020, and on auxiliary requests 8 and 9 filed during the oral proceedings on 13 and 14 April 2022.

II. Claim 1 was identical in the main request and auxiliary request 1, and related to:

"A method of preparing a sterile and injectable composition, the method comprising at least the steps of:
a) providing at least one gel of a hyaluronic acid or a salt thereof, said hyaluronic acid being selected from a crosslinked hyaluronic acid form, a non-crosslinked hyaluronic acid form or a mixture thereof;
b) adding to said gel of hyaluronic acid at least mepivacaine hydrochloride as anaesthetic agent; and
c) sterilizing the mixture obtained in step b)."

Claim 1 was identical in auxiliary requests 2 and 3 and differed from claim 1 of the main request by the

additional feature that sterilizing step c) was carried out "by thermal means".

Claim 1 was identical in auxiliary requests 4 and 5 and differed from claim 1 of the main request by the additional feature that the composition was "a sterile and injectable soft filler composition for filling of volume defects of the skin, in particular the filling of wrinkles," (additions emphasised by the Board).

Claim 1 was identical in auxiliary requests 6 and 7 and combined the amendments of auxiliary requests 2/3 and 4/5.

Claim 1 of auxiliary request 8 differed from claim 1 of the main request by the addition of the following feature: "and wherein the composition comprises from 1 to 3% by weight of hyaluronic acid, relative to the total weight of the composition, and from 0.05 to 3% by weight anaesthetic agent(s), based on the total weight of the composition".

Claim 1 of auxiliary request 9 differed from claim 1 of the main request in that the hyaluronic acid was limited to "a mixture of a crosslinked hyaluronic acid form and a non-crosslinked hyaluronic acid form"

III. The followed documents cited in the appealed decision are relevant here:

D2: WO 2012/104419 A1
D8: Kamran Samii, "Anesthésie Réanimation chirurgicale", Médecine-Sciences Flammarion, 2003
D9: Albrecht, "Manuel pratique d'anesthésie" Masson, 2009

D12: Bouaziz H. at al., "La mepivacaine doit-elle remplacer la lidocaine ?" MAPAR 1999, 193-197
D13: WO 2015/097261 A1

IV. The opposition division decided the following:

The subject-matter of the main request lacked novelty over the method of D2 (claim 36) with the single selection of mepivacaine as anaesthetic (hereinafter embodiment a)). The opposition division reasoned that, to put the teaching of claim 36 into practice, the methods of the examples would be followed accordingly and mepivacaine hydrochloride would be used.

Likewise, none of the auxiliary requests 1-8 met the requirements of novelty.

The subject-matter of auxiliary request 9 was novel because D2 did not show a process as claimed wherein a mixture of crosslinked and non-crosslinked hyaluronic acid is used. As to inventive step, the embodiment a) held prejudicial to novelty for the main request was not considered to be a realistic springboard, because D2 did not exemplify gels with mepivacaine or would particularly suggest mepivacaine as anaesthetic. Starting instead from the examples of D2 comprising lidocaine as anaesthetic, the problem to be solved was to provide a process which resulted in less degradation of the hyaluronic acid gel. The claimed solution involved an inventive step.

V. In the course of the appeal proceedings, the appellant - proprietor maintained the main request and auxiliary requests 1-8 underlying the decision (see II. above), filed a new auxiliary request 9 with the grounds of appeal, renumbered auxiliary request 9 underlying the

decision as auxiliary request 10, and further filed auxiliary request 11 with the reply dated 26 January 2023.

Claim 1 of auxiliary request 9 differed from claim 1 of the main request in that the alternative wherein the hyaluronic acid is non-crosslinked was deleted.

Claim 1 of auxiliary request 11 combined the limitations of auxiliary requests 2/3 ("by thermal means") with those of auxiliary request 10 ("a mixture of a crosslinked hyaluronic acid form and a non-crosslinked hyaluronic acid form").

VI. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VII. Oral proceedings were held before the Board in the presence of the appellant - proprietor and appellant - opponent 3.

VIII. The appellant - proprietor's arguments can be summarised as follows:

D2 did not disclose the subject-matter of claim 1 of the main request.

To arrive at a method for providing a hyaluronic acid composition comprising mepivacaine starting from claim 36 of D2, two selections were needed, namely selecting a local anaesthetic between amide type local anaesthetics and ester type anaesthetics, and selecting mepivacaine as a specific amide type local anaesthetics. Mepivacaine was conceptually cited in a list of 36 anaesthetics without being emphasised, exemplified or reduced to practice in D2. Furthermore,

at the filing date of D2, the skilled person was refrained based on its knowledge to prepare compositions comprising mepivacaine, considering its pKa and the resulting high risk of precipitation, as confirmed by D13. Thus D2 did not disclose clearly and unambiguously a method for providing a hyaluronic acid composition comprising mepivacaine.

The claimed method further differed from the teaching of D2 in that:
- mepivacaine was used in its hydrochloride form, and
- mepivacaine hydrochloride was specifically added to a gel of hyaluronic acid.

Accordingly, regarding inventive step, only the examples of D2 comprising lidocaine hydrochloride or bupivacaine could be seen as promising springboards to the invention. Considering the similar physicochemical properties of lidocaine and mepivacaine, the most promising springboard was the embodiment comprising lidocaine hydrochloride. The technical problem starting from this lidocaine embodiment was to provide a method for preparing a sterile and injectable hyaluronic acid composition comprising an anaesthetic which resulted in less degradation upon sterilization. The solution involved an inventive step.

IX. The arguments of appellants - opponents 2 and 3 can be summarised as follows:

The appealed decision identified three possible starting points within the disclosure in D2, namely:
a) claim 36 in combination with the selection of mepivacaine;
b) the examples comprising lidocaine as anaesthetic; and

c) the examples comprising bupivacaine as anaesthetic.

There was however no justification for the opposition division's conclusion that embodiment a) was an unrealistic starting point. There was no requirement in the case law for there to be a worked example of an embodiment in order for that embodiment to be considered as representative of the closest prior art. Furthermore, the use of mepivacaine as an anaesthetic agent was mentioned in D2, and mepivacaine was a well-known anaesthetic agent at the priority date of the patent. Lastly, it was established case law that if the skilled person had a choice of several workable routes which might lead to the claimed invention, the rationale of the problem-solution approach required that the invention be assessed relative to all of these possible routes. If the invention was obvious in respect of at least one of those routes, then an inventive step was lacking.

Starting from embodiment a), the objective technical problem was the provision of an alternative method for preparing a hyaluronic acid composition. The claimed method lacked an inventive step. No prejudice had been demonstrated to exist against the use of mepivacaine in hyaluronic acid compositions.

X. The appellant - proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-8 on file, auxiliary request 9 submitted with the grounds of appeal, auxiliary request 10 corresponding to auxiliary request 9 on file, or auxiliary request 11 filed on 26 January 2023.

XI. The appellants - opponents 2 and 3 both requested that the decision under appeal be set aside and that the patent be revoked.

XII. Opponent 1 is party as of right in the present appeal proceedings and did not make any submission.

Reasons for the Decision

1. Main request, inventive step

1.1 Choice of the starting point

1.1.1 The invention in the patent in suit relates to the field of sterile and injectable compositions comprising hyaluronic acid, especially soft tissue filler compositions, and is directed to a method of preparing such compositions, comprising in particular the addition of mepivacaine hydrochloride as anaesthetic agent. The patent mentions among other properties that a filler composition obtained according to the method of the invention, including mepivacaine hydrochloride as anaesthetic agent, may be sterilized without significantly affecting the stability of the hyaluronic acid gel (see e.g. paragraph [0027]).

1.1.2 D2 is also concerned with the provision of injectable hyaluronic acid compositions comprising a hyaluronic acid and an anaesthetic agent. The compositions of D2 additionally contain an ascorbic acid derivative in an amount which prevents or reduces the effect on the viscosity and/or elastic modulus G' of the composition caused by the local anaesthetic upon sterilisation by heat (see the abstract). D2 thus belongs to the same field of anaesthetic-containing filler compositions and

addresses the same problem of (rheological) stability upon sterilisation.

1.1.3 Within D2, three different starting points were debated by the parties:
a) the method of claim 36 of D2 as applied to mepivacaine (see 1.1.4 below);
b) the examples of D2 comprising lidocaine hydrochloride as anaesthetic (e.g. example 1);
c) the examples of D2 comprising bupivacaine as anaesthetic (see example 6).

1.1.4 Regarding the above embodiment a), claim 36 of D2 generally discloses a method of manufacturing a hyaluronic acid composition comprising:
a) mixing
-a hyaluronic acid,
- a local anaesthetic selected from the group consisting of amide and ester type local anaesthetics or a combination thereof, and
- an ascorbic acid derivative in an amount which prevents or reduces the effect on the viscosity and/or elastic modulus G' of the composition caused by the local anaesthetic upon sterilization by heat, and
b) subjecting the mixture to sterilization by heat.

Mepivacaine is explicitly disclosed in the list of suitable anaesthetics recited in D2 (see page 8, line 17; see also claim 8). An embodiment of the method of claim 36 wherein the local anaesthetic is mepivacaine thus results from a single selection in D2 and is part of the direct and unambiguous disclosure of D2. Contrary to the appellant - proprietor's view, it is for that purpose not required to additionally make a selection among amide and ester type local

anaesthetics, because the single selection of mepivacaine necessarily means that the anaesthetic belongs to the amide group comprising mepivacaine, and is sufficient to arrive at the above mepivacaine embodiment.

In other words, a method comprising mixing a hyaluronic acid, mepivacaine and an ascorbic acid derivative, and then subjecting the mixture to sterilization by heat, belongs to the state of the art.

1.1.5 Under Article 56 EPC, an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. The state of the art is as defined in Article 54(2) EPC.

In the case at hand, the opposition division concluded that the subject-matter of the main request and auxiliary requests 1-8 was anticipated by the method of claim 36 of D2 as applied to mepivacaine, and thus clearly considered this embodiment a) to belong to the state of the art under Article 54(2) EPC. Nonetheless, the opposition division disregarded the same embodiment a) as starting point for the assessment of inventive step, for lack of an example or pointer to this embodiment. The appellant - proprietor also submits that embodiment a) is not a suitable starting point for the assessment of inventive step.

The Board does not concur with these positions.

There is no requirement in the case law that an embodiment of the state of the art must be exemplified for it to be considered in the assessment of inventive step. There is likewise no requirement that the prior

art contains any pointer, suggestion or incentive to select a particular embodiment for further development for this embodiment to qualify as a starting point in the problem solution approach.

The criteria developed in the case law are mainly that the starting point, or "closest prior art", is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see the Case Law of the Boards of Appeal, 10th edition, 2022, I.D.3.1). These is no debate that D2, including any of its embodiments a)-c) identified above, meet these criteria.

But beyond these broad criteria, it is also established case law that, if the skilled person has a choice of several workable routes which might lead to the invention, the rationale of the problem and solution approach requires that the invention be assessed relative to all these possible routes, before an inventive step can be acknowledged. Conversely, if the invention is obvious to the skilled person in respect of at least one of these routes, then an inventive step is lacking. If an inventive step is to be denied, the choice of starting point needs no specific justification, because the claimed invention must be non-obvious having regard to any prior art (see T 261/19, point 2.5 of the reasons; T 1112/19, point 2.1.3; T 574/19, point 2.2.3).

1.1.6 The Board further considers that the disclosure in D2 relating to mepivacaine is neither defective nor speculative. Contrary to the appellant - proprietor's view, no prejudice is shown to have existed at the

relevant date against the use of mepivacaine in hyaluronic acid compositions. The sole document on which the appellant - proprietor based this argument is D13 (see paragraphs [0028]-[0031]), which is a single patent application document originating from appellant - opponent 3 and filed after the filing date of the patent in suit. D13 is not suitable for establishing the existence of a prejudice, i.e. a widely held but incorrect opinion of a technical fact, at the relevant date.

The mere fact that the use of mepivacaine is not exemplified does not mean either that D2 is speculative or not enabled in this respect. This is because D2 discloses examples showing the successful use of other anaesthetics, namely bupivacaine, tetracaine and, especially, the closely related lidocaine, whose physicochemical and pharmaceutical properties are very similar to those of mepivacaine, as shown in D8 (see Table 8-1) and D9 (see page 144). Considering in particular that the pKa of mepivacaine is barely different from that of lidocaine (7.6 vs 7.7 according to D8), the appellant - proprietor's argument regarding the expected unsuitability of mepivacaine for the preparation of hyaluronic acid - anaesthetics compositions due to its pKa and the resulting high risk of precipitation, is not convincing. The observation in D2 that anaesthetics other than benzocaine are weak bases with pKa values mainly in the range 8-9 does not give cause to expect any more problems with mepivacaine than with the exemplified lidocaine (see D2, page 7, line 35 to page 8, line 2). On the contrary, the same passage indicates that, as a result of their similarity, these anaesthetics "may be expected to have similar chemical and physical effects on the hyaluronic acid composition". There is accordingly no reason to

regard the mention of mepivacaine in D2 as an unrealistic starting point.

Lastly, even if, at the filing date of the patent, only dermal fillers comprising lidocaine hydrochloride were marketed, the prior art for the assessment of inventive step is not limited to such marketed products.

For these reasons, the above embodiment a), i.e. the method of claim 36 of D2 as applied to mepivacaine, is taken as starting point for the assessment of inventive step.

1.2 Differences

Starting from this general method of claim 36 of D2 as applied to mepivacaine, the method of claim 1 of the main request differs by:
- the specific use of mepivacaine hydrochloride as anaesthetic, and by
- the specific order of addition required by step b of claim 1, namely the addition of mepivacaine *to* a gel of hyaluronic acid.

In this respect, the Board concurs with the appellant - proprietor that these features are neither expressly mentioned in D2 in relation with mepivacaine, nor derivable from the examples, wherein anaesthetics other than mepivacaine are used. A combination of the general teaching of claim 36, as applied to the mepivacaine alternative of page 8, with some features of the examples using other anaesthetics would amount to combining features from separate embodiments in D2, and would not meet the condition that, for an item to be part of the state of the art, the claimed features in combination must be directly and unambiguously

derivable from the prior art. While it may be obvious to use the conditions and salt form shown for lidocaine when putting the teaching of claim 36 as applied to mepivacaine into practice, this does not suffice for D2 to anticipate claim 1.

Thus, the order of addition, i.e. the addition of mepivacaine *to* a gel of hyaluronic acid, can neither be directly derived from the impermissible combination of separate items of D2 (namely the lidocaine examples and the mention of mepivacaine on page 8), nor does it implicitly, i.e. inevitably, follow from the general teaching of claim 36 of D2, since a process whereby hyaluronic acid is swelled with a solution already comprising the mepivacaine anaesthetic is also conceivable.

Likewise, the use of mepivacaine hydrochloride is neither expressly disclosed in D2 nor is the inevitable result of carrying out the teaching of D2. Page 8 of D2 merely recites "mepivacaine" without specifying that it is in the form of a salt, let alone a hydrochloride. Even if it were assumed that a salt must be used because the free base would be water insoluble, there is no direct and unambiguous teaching in D2 that this salt must have received regulatory approval, i.e. be the hydrochloride.

1.3 Technical problem

No particular technical effect has been shown to arise from the choice of the claimed order of addition, or the selection of the hydrochloride salt. The appellant - proprietor, while contesting that the above embodiment a) would be a suitable starting point, did not allege that the claimed process would achieve any

particular advantage in case embodiment a) was taken as starting point for the assessment of inventive step. The comparative data relied on by the appellant - proprietor (see in particular examples 1 and 2 of the patent) aim to show an improved stability upon sterilization resulting from the choice of mepivacaine over the known lidocaine compositions, but they are not relevant to the present approach where the composition of embodiment a), which already contains mepivacaine, is chosen as starting point. The same conclusion applies to the data presented in D13 (see tables 1-6 and 25; paragraphs [0415] and [0429]): there is no demonstration of any technical effect finding its origin in the differentiating features in this case, namely the order of addition and the choice of the hydrochloride salt for mepivacaine.

Consequently, the technical problem to be solved is the provision of an alternative method for preparing a hyaluronic acid composition.

1.4 Obviousness

For the reasons given above (see 1.1.5 and 1.1.6), the disclosure in D2 of a method for the preparation of mepivacaine-containing hyaluronic acid compositions is neither speculative nor deficient, and the skilled person has no ground to expect any particular difficulty in carrying out this teaching of D2. There is no convincing reason why the skilled person would not elect to start from this embodiment a).

Since embodiment a) is disclosed in a general manner in D2, a skilled person seeking to implement this method would in an obvious manner choose the conditions and the type of salt as used in the examples of the same

document in the context of other anaesthetics, such as lidocaine (see e.g. claim 1). In these examples, lidocaine is employed in the form of a hydrochloride salt, and the order of addition is as defined in claim 1, namely the anaesthetic is added to the gel of hyaluronic acid. The skilled person, starting from D2 and putting the general method of claim 36 as applied to mepivacaine into practice, would, without exercise of any inventive skill, apply to mepivacaine these conditions shown for lidocaine and would thereby expect to solve the above technical problem, which is merely the provision of an alternative.

Lastly, the common general knowledge that mepivacaine is more costly than lidocaine (see D12, last page) is a foreseeable disadvantage which does not confer an inventive step to the claimed method.

Accordingly, the main request does not meet the requirements of inventive step.

2. Auxiliary requests

2.1 In auxiliary requests 1-6, claim 1 does not comprise any additional differentiating feature over embodiment a) of D2, and the same conclusion of lack of inventive step applies:

- claim 1 of auxiliary request 1 is identical to claim 1 of the main request;

- the additional feature of claim 1 of auxiliary requests 2 and 3, namely that sterilizing step c) is carried out "by thermal means", is disclosed in claim 36 of D2 ("sterilization by heat");

- in claim 1 of auxiliary requests 4 and 5, the definition of the composition as a "soft filler composition for filling of volume defects of the skin, in particular the filling of wrinkles" does not differentiate it from D2 (see page 15 of D2, line 32-36);

- the combination of the above limitations in claim 1 of auxiliary requests 6 and 7 does not establish any additional difference either.

2.2 Claim 1 of auxiliary request 8 differs from the main request by the addition of the following feature: "and wherein the composition comprises from 1 to 3% by weight of hyaluronic acid, relative to the total weight of the composition, and from 0.05 to 3% by weight anaesthetic agent(s), based on the total weight of the composition".

Following the reasoning presented above for the main request, the skilled person, seeking to solve the problem of providing an alternative, and putting the method of claim 36 as applied to mepivacaine in practice, would follow the conditions described in the examples for e.g. lidocaine, and would accordingly use the same or similar amounts of hyaluronic acid (2%) and anaesthetic agent (0.3%). These amounts therefore do not involve an inventive step.

2.3 In claim 1 of auxiliary request 9, the hyaluronic acid is limited to:
- a crosslinked hyaluronic acid form or
- a mixture of a crosslinked hyaluronic acid form and a non-crosslinked hyaluronic acid form.
In claim 1 of auxiliary request 10, the hyaluronic acid is further limited to the above mixture.

The appellant-proprietor did not demonstrate that these particular forms of hyaluronic acid lead to any particular technical effect. Accordingly, the technical problem to be solved remains the provision of an alternative method for preparing a hyaluronic acid composition. The claimed solution is obvious, because the use of a crosslinked hyaluronic acid gel comprising a portion of hyaluronic acid which is not crosslinked is explicitly suggested in D2 (see page 7, lines 11-20). The requirements of Article 56 EPC are thus not met by auxiliary requests 9 and 10 either.

2.4 Auxiliary request 11 combines the amendments of auxiliary requests 2 (sterilisation step c) "by thermal means") and auxiliary request 10 (hyaluronic acid being a mixture of crosslinked and non-crosslinked forms), and lacks an inventive step for the same reasons.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos D. Boulois

Decision electronically authenticated