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Datasheet for the decision of 29 May 2024

Case Number: T 1634/22 - 3.3.04

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Language of the proceedings: EN

Title of invention:

Compositions comprising amino acids for use in the treatment of mucositides in neoplasia patients undergoing radiation therapy and/or chemotherapy

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - (no)

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Case Number: T 1634/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 May 2024

Appellant: (Opponent)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Wohlfahrt, Jan Günther Gleiss Große Schrell und Partner mbB Patentanwälte Rechtsanwälte Leitzstraße 45 70469 Stuttgart (DE)
Respondent: (Patent Proprietor)	Professional Dietetics S.p.A. Via Ciro Menotti, 1/A 20129 Milano (MI) (IT)
Representative:	Cesa, Roberta Buzzi, Notaro & Antonielli d'Oulx S.p.A. Corso Vittorio Emanuele ll, 6 10123 Torino (IT)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 April 2022 rejecting the opposition filed against European patent No. 3294279 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 294 279 (the patent in suit) was granted with ten claims. Claim 1 reads as follows:

> *1. Amino acid composition for use in the treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy or radio chemotherapy,*
>
> *the composition comprising an active agent, said active agent comprising the amino acids glutamine, leucine, isoleucine, valine, lysine, threonine, histidine, phenylalanine, methionine, tryptophan, tyrosine, and cystine,*
>
> *wherein the glutamine:leucine weight ratio is comprised in the range 4.3 to 5.3.*

II. The patent in suit was opposed under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. The patent proprietor requested that the opposition be rejected and that the patent be maintained as granted (main request). It also filed a number of amended sets of claims as auxiliary requests.

IV. The documents cited in the proceedings before the opposition division included the following:

D3: Otolaryngology - Head and Neck Surgery 121(4), 348-354 (1999)

D6: South Asian Journal of Cancer 3(1), 8-12 (2014)

D7: Clinical Nutrition 33, 694-701 (2014)

V. The decision under appeal is the opposition division's decision rejecting the opposition, announced on 7 April 2022 and posted on 29 April 2022.

VI. According to the decision under appeal, the subject-matter of the claims as granted met the requirements of sufficiency of disclosure (Article 100(b) EPC) and novelty (Articles 100(a), 52(1) and 54 EPC).

Inventive step was assessed starting from the disclosure of document D6, which was deemed to represent the closest prior art. D6 related to the use of glutamine for the same therapeutic purpose as identified in claim 1 of the main request, namely the alleviation and prevention of radiation-induced oral mucositis. The objective technical problem was the provision of an alternative amino acid-based composition that was effective in the treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy and/or radio chemotherapy. Based on the cited prior art and common general knowledge, the person skilled in the art seeking to solve the objective technical problem would not have been in a position to formulate the composition according to claim 1 without inventive skill (Articles 100(a), 52(1) and 56 EPC).

VII. The opponent (appellant) filed an appeal against this decision.

VIII. With its reply to the appeal, the patent proprietor (respondent) filed the sets of claims of a main request and eight auxiliary requests.

The claims of the **main request** are identical to the claims as granted.

Claim 1 of **auxiliary request 1** is identical to claim 1 as granted, except that it specifies that the active agent comprises the amino acids *"in free form"*.

Claim 1 of **auxiliary request 2** is identical to claim 1 as granted, except for the added requirement: *"wherein said active agent is free of arginine"*.

Claim 1 of **auxiliary request 3** is identical to claim 1 as granted, except for the added requirement: *"wherein said active agent is free of serine, proline, glycine, alanine, glutamic acid".*

Claim 1 of **auxiliary request 4** is identical to claim 1 as granted, except for the added requirement: *"wherein said active agent is free of arginine, serine, proline, glycine, alanine, glutamic acid".*

Claim 1 of **auxiliary request 5** is identical to claim 1 as granted, except that it specifies that the active agent consists of (instead of comprises) the listed amino acids.

Claim 1 of **auxiliary request 6** is identical to claim 1 as granted, except that it specifies: *"wherein the composition is free of any other amino acids"*.

Claim 1 of **auxiliary request 7** is identical to claim 1 as granted, except for the additional requirement: *"wherein the amino acids included in the composition consist of the amino acids of the active agent".*

Claim 1 of ***auxiliary request 8*** is identical to claim 1 as granted, except that it specifies that the active agent comprises the amino acids *"in free form"* and that *"the composition is free of any other amino acids"*.

IX. In a communication under Article 15(1) RPBA issued in preparation for oral proceedings and advising the parties of its preliminary opinion, the board noted that the appellant did not pursue its objection relating to a lack of novelty in its grounds of appeal. The board was of the preliminary view that the appellant's objection of insufficient disclosure would not succeed. The board also observed that no comparative data in relation to the composition described in the closest prior art D6 was on file. Starting from the disclosure of document D6, the objective technical problem in relation to claim 1 of the main request was to provide an alternative glutamine formulation for use in the treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy or radiation chemotherapy.

X. The appellant advised the board that it would not be attending the oral proceedings.

XI. Oral proceedings before the board took place on 29 May 2024 in the form of a videoconference, in the absence of the duly summoned appellant.

XII. The appellant's arguments in relation to inventive step, as far as they are relevant to the present decision, can be summarised as follows:

The appellant agreed with the opposition division's finding that document D6 represented the closest prior art. The composition of claim 1 as granted differed from the disclosure of D6 by combining glutamine with further specified amino acids and by the specified weight ratio of glutamine to leucine. No specific technical effect had been shown in association with the distinguishing technical features.

The appellant agreed with the opposition division's formulation of the objective technical problem as being the provision of an alternative amino acid-based composition that was effective in the treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy and/or radio chemotherapy.

The appellant disagreed with the opposition division's finding of non-obviousness. In order to provide an alternative composition, the distinguishing technical features did not have to contribute to the effect of glutamine as shown in D6; it was merely required that they did not preclude the effect of glutamine.

In this regard, there was no teaching or technical prejudice in the prior art that would have led the person skilled in the art to avoid combining glutamine with the further amino acids listed in claim 1, in order to provide alternative compositions for treating mucositis.

On the contrary, it might even have been hoped that additional therapeutic and nutritional benefits could be obtained. For instance, it would have been obvious to combine glutamine with essential amino acids, or amino acids for which there was a recommended daily intake (e.g. those listed in claim 1), in view of their generally known nutritional benefit. The chosen ratio of glutamine to leucine was arbitrary and consequently could not contribute to inventive step.

XIII. The respondent's arguments can be summarised as follows:

Inventive step - main request

The distinguishing technical features relating to a specific combination of amino acids and to the ratio of

glutamine to leucine were functionally interrelated and provided technical effects achieved by the composition in its entirety.

The cited prior art did not suggest that a specific combination of amino acids could have produced the effects disclosed in the patent or that such a combination might be useful in the treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy or radio chemotherapy (see the reply to the appeal, page 5, last paragraph).

As far as the advantages of the claimed composition were concerned, reference was made to the application as filed, page 2, lines 12 to 28, page 3, lines 11 to 27 and Table 6 (corresponding to paragraphs [0007] and [0012]-[0014] and Table 6 in the patent in suit). In addition to the beneficial effect on severe mucositis, the claimed composition provided an anti-inflammatory effect. Clinical data also showed a general maintenance of the most important blood parameters related to catabolism (contrary to what had been reported, for a dosage of 30 g glutamine alone, in reference [8] of the patent). Using amino acids in free form allowed producing such compositions at low cost in comparison with synthetic proteins and growth factors. These advantages had not been described in the prior art.

Even if the objective technical problem were to be formulated as being the provision of an alternative composition for use in the treatment of mucositis, a pointer in the prior art would have been needed for the skilled person to arrive at the modifications made in accordance with claim 1 as granted in comparison with the glutamine-only composition disclosed in D6.

No such pointer was provided in the cited prior-art documents.

At the time of priority there was not even consensus on the use of glutamine being beneficial, as shown by documents D3 and D6.

The person skilled in the art would have known to avoid adding further components to a medicament, as this could impair the effect of the active agent. In particular, it was also general knowledge that combining other amino acids with glutamine could alter the function of glutamine. Document D7 showed, for instance, on page 699 that the combination of arginine with glutamine inhibited the effects of the latter.

Auxiliary requests

The auxiliary requests were identical to those filed in the proceedings before the opposition division. They were intended to define the claimed invention more precisely, in order to address any objections under Article 100(a) and (b) EPC. Concerning the issue of inventive step starting from the disclosure of D6, the same reasoning applied to claim 1 of auxiliary requests 1 to 8 as that set out with respect to claim 1 of the main request. As mentioned in the patent in suit, avoiding the presence of the amino acids serine, proline, glycine, alanine, glutamic acid and arginine, which could be counterproductive or even harmful, represented a further advantage (see page 9, lines 4 to 8, of the application as filed or paragraph [0048] in the patent in suit).

XIV. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

XV. The respondent (patent proprietor) requested that the appeal be dismissed, or, in the alternative, that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 8 filed with the reply to the statement setting out the grounds of appeal.

Reasons for the Decision

1. Oral proceedings, absence of the appellant

1.1 In conformity with Rule 115(2) EPC and Article 15(3) RPBA, the oral proceedings before the board took place in the absence of the appellant, which had been duly summoned and had advised the board that it would not be attending (see point X. above).

1.2 The appellant was treated as relying only on its written case (Article 15(3) RPBA).

2. Claim construction

2.1 The term "amino acid composition" would be commonly understood to refer to a composition containing free amino acids. A protein would not be regarded as an "amino acid composition".

2.2 It would appear that the opposition division understood the wording "said active agent comprising the amino acids ..." to mean that all of the listed amino acids must contribute to the therapeutic effect of treating mucositis (see the decision under appeal, Reasons 2.3.5, page 14, fourth paragraph).

The board is of the view that the wording in claim 1 does not actually require this. Rather, it is the "active agent" of claim 1 which (by definition) has

the claimed therapeutic efficacy. This "active agent" is defined as a composition comprising the listed amino acids. The terms of the claim are met if at least one of the amino acids provides the effect. The components of the active agent include glutamine, a compound known to have the desired therapeutic efficacy.

3. Inventive step - main request
(Articles 100(a), 52(1) and 56 EPC)

Patent in suit

3.1 The patent in suit aims to provide amino acid-based compositions for use in the treatment of mucositis induced by radiotherapeutic and/or chemotherapeutic treatments, in patients suffering from neoplasia of the cervical-cephalic region (see paragraphs [0001], [0002] and [0009] of the patent in suit).

3.2 A clinical study is presented as evidence of the composition's therapeutic benefit (paragraphs [0024] to [0029], [0053] to [0061] and [0072] to [0079]).

3.3 Claim 1 as granted defines a composition with an active agent comprising glutamine and eleven further specified amino acids, with a defined weight ratio of glutamine to leucine in the range of 4.3 to 5.3.

Starting point in the prior art

3.4 The appellant's objection in relation to a lack of inventive step of claim 1 as granted is based on an approach starting from the disclosure of document D6.

3.5 D6 relates to a prospective randomised study investigating the role of oral glutamine in the alleviation and prevention of radiation-induced oral mucositis in head and neck malignancy patients (see D6: title and abstract). Seventy biopsy-proven patients

with head and neck cancer receiving primary or adjuvant radiation therapy were randomised to receive either an oral glutamine suspension daily two hours before radiation in the study arm (10 g glutamine in 1000 ml of water, n=35) or nothing before radiation in the control arm (n=35) (see the abstract). 32 patients in the study arm developed mucositis. The mean time of onset of mucositis was significantly delayed in the study arm in comparison to that in the control arm. The occurrence and duration of grade 3 and grade 4 mucositis were significantly less in the study arm. The authors of D6 conclude that glutamine delays radiation-induced oral mucositis in head and neck cancer patients and, moreover, it reduces the frequency and duration of grade 3 and grade 4 mucositis (D6: abstract; page 9, "Materials and Methods" and "Results and Analysis"; page 10, Tables 2, 3 and 4; page 11, last paragraph).

Distinguishing technical feature

3.6 The composition of claim 1 of the main request differs from the composition used in the study of D6 by also containing, in addition to glutamine, leucine, isoleucine, valine, lysine, threonine, histidine, phenylalanine, methionine, tryptophan, tyrosine and cystine, the weight ratio of glutamine to leucine being in the range of 4.3 to 5.3.

Technical problem and solution

3.7 In the clinical study described in the patent in suit, the study group received a composition according to claim 1 and was compared to a control group of untreated patients (paragraph [0024] on page 5, line 6, and paragraph [0054] on page 7).

3.8 In the study arm of the clinical study described in D6, crystalline glutamine was dissolved in water and administered within the two hours before radiation.

3.9 As conceded by the respondent, there is no comparative data on file comparing the therapeutic efficacy of a composition according to claim 1 with that of glutamine alone (i.e. the starting point in the prior art).

3.10 Hence, no effect associated with the presence of the additional amino acids (in the case of leucine in a specific ratio to glutamine) has been shown in comparison with the composition of D6.

Moreover, it has not been shown that any of the additional amino acids, or a combination thereof, have therapeutic efficacy against mucositis.

Furthermore, it is not apparent that any particular technical effect can be attributed to the chosen ratio of glutamine to leucine. The respondent conceded that no evidence was on file that showed a specific technical effect in relation to this feature.

Thus, it cannot be confirmed that the added amino acids have any specific benefit in comparison with glutamine monotherapy.

3.11 In relation to the assertion in paragraph [0077] of the patent in suit that the blood parameters shown in Table 6 represent an improvement in comparison with the values reported in reference [8] of the patent in suit for a dosage of 30 g of glutamine alone, the following observations may be added:

As pointed out by the board in its communication under Article 15(1) RPBA, and as previously pointed out by the opposition division (see the decision under appeal, last paragraph of point 2.3.1.1), reference [8] as cited in the patent in suit is not on file in the

present proceedings. Hence, its alleged content and conclusions cannot be verified, *inter alia* in terms of the statistical significance of its results. According to paragraph [0077] of the patent in suit, the dosage of glutamine administered in the study of reference [8] was also different from the dosage used in the study of D6. The assertion in the patent in suit with respect to the contents of reference [8], and in particular about how its results may compare to the results reported in Table 6, does not have any probative value amounting to the level of a correct comparative experiment in relation to D6. Thus, no improvement attained by administration of the claimed composition in comparison with the composition of D6 was shown.

3.12 In conclusion, it has not been shown that the effects mentioned by the respondent during the oral proceedings before the board (such as an anti-inflammatory effect or an alleged favourable development of certain haematological parameters) can be attributed to a technical feature distinguishing the claimed composition from the product according to D6.

3.13 The alleged cost advantage of using free amino acids in comparison to synthetic proteins is irrelevant as it is not based on a technical feature distinguishing the claimed composition from that disclosed in D6.

3.14 What the data presented in the patent in suit shows is that a composition according to claim 1 has efficacy against mucositis in the relevant patient group (see paragraph [0072] and Table 5). This has not been contested by the appellant.

3.15 Hence, starting from the disclosure of document D6, the objective technical problem is to provide an alternative glutamine formulation for use in the

treatment of mucositis in patients suffering from neoplasia of the cervical-cephalic region and undergoing radiation therapy or radiation chemotherapy.

3.16 What has to be established is whether the person skilled in the art seeking to solve this technical problem would have found it obvious to provide a composition as defined in claim 1 instead of just glutamine for this purpose.

Obviousness of the solution

3.17 The glutamine formulation in question is a pharmaceutical product for alleviating oral mucositis, a side effect of cancer treatment. Any alternative product should have efficacy against oral mucositis at a useful level.

3.18 In order to solve the technical problem of providing an alternative composition, the person skilled in the art would have considered modifying the composition by adding further pharmacologically acceptable components. In the absence of a technical prejudice or disincentive in relation to any particular component, no pointer in the prior art would have been required in order for the person skilled in the art to consider adding this component.

3.19 Since the respondent did not show the existence of a technical prejudice, the board does not agree with the respondent's view that a pointer in the prior art would have been required for combining glutamine with the further amino acids listed in claim 1 as granted.

3.19.1 In view of the objective technical problem, an unspecified general caution about adding further components to any medicament because they might detract from the product's efficacy (as argued by the

respondent) is too vague to provide a pertinent technical prejudice.

3.19.2 For more specific evidence, the respondent referred to document D7, which reports that glutamine supplementation, but not combined glutamine and arginine supplementation, improved gut barrier function during chemotherapy-induced intestinal mucositis in rats. In the respondent's view, this at least showed that other amino acids could have undesirable effects.

As conceded by the respondent, this line of argument was submitted for the first time at the oral proceedings, and D7 was cited for the first time in this specific context also only at the oral proceedings before the board. Thus, the admittance of this line of argument would have to be based on exceptional circumstances, which are not apparent in the case at hand (Article 13(2) RPBA).

In any case, however, D7 does not relate to any of the amino acids in claim 1. It relates to a different clinical context, and to rats rather than human subjects. Moreover, as a specialised journal article D7 cannot be considered to represent common general knowledge. This line of argument, therefore, does not amount to evidence of a technical prejudice against combining glutamine with further amino acids in general, or specifically with any of the amino acids listed in claim 1 as granted, in the context of the treatment in claim 1.

3.20 The additional amino acids listed in claim 1 were known to be physiologically compatible as they are established - even essential - nutritional components.

3.21 In the circumstances of the case at hand, i.e. in the absence of any technical prejudice, no pointer in the

prior art would have been required for the person skilled in the art to consider modifying the glutamine formulation by adding the amino acids listed in claim 1, as arbitrary physiologically compatible components. The weight ratio of glutamine to leucine is a further arbitrary feature, and as such cannot provide a basis for an inventive step.

3.22 The respondent's further argument that it was not even established at the time of priority that glutamine could be used in the treatment of radiation-induced oral mucositis is factually incorrect since the starting point in the prior art as disclosed in D6 is precisely the use of glutamine in the treatment of radiation-induced oral mucositis as demonstrated in a clinical study.

Document D3 cited by the respondent in this context predates D6 by fifteen years, and the authors of D3 themselves conclude that their findings - which did not confirm the concern that glutamine supplementation might increase tumour growth - are encouraging for the continued use of glutamine supplements in patients with head and neck squamous cell carcinoma (D3: Abstract and Conclusions).

D6 itself mentions pre-published literature (a pilot study and a pre-published review article) according to which the administration of oral glutamine may significantly reduce the duration and severity of objective oral mucositis during radiotherapy. The study described in D6 was conceived as an adequately powered randomised clinical study to further establish these findings (D6: page 9, left-hand column, second paragraph), and indeed confirmed the efficacy of glutamine (D6: page 11, Conclusion).

3.23 For these reasons, the subject-matter of claim 1 as granted does not involve an inventive step within the meaning of Article 56 EPC.

4. Inventive step - auxiliary requests (Articles 52(1) and 56 EPC)

Auxiliary request 1

4.1 In view of the meaning of the term "amino acid composition" as set out in point 2.1 above, the scope of claim 1 of auxiliary request 1, which specifies that the active agent comprises the amino acids "in free form", is identical to that of claim 1 of the main request. As a consequence, the same reasoning and conclusions in respect of inventive step apply as those set out in section 3 above.

Auxiliary requests 2 to 8

4.2 As in claim 1 of auxiliary request 1 (see point 4.1), the feature "in free form" in claim 1 of auxiliary request 8 is redundant.

4.3 The further features added in each case in amended claim 1 of auxiliary requests 2 to 8 require the absence of arginine, serine, proline, glycine, alanine, glutamic acid, or of amino acids other than those listed in the claim, from the active agent or composition.

The study medication in the closest prior art D6 contains only glutamine and water. It does not contain any amino acids other than glutamine.

Thus, the additional features according to auxiliary requests 2 to 8 do not further distinguish the claimed subject-matter from the composition disclosed in the closest prior art D6, and therefore they cannot

contribute anything to inventive step. According to the problem-and-solution approach, a technical effect or advantage (such as the alleged advantage of avoiding potentially harmful components) can only be taken into account in the assessment of inventive step if it is associated with a technical feature distinguishing the claimed subject-matter from the disclosure of the closest prior art.

4.4 For these reasons, the reasoning and conclusion in respect of inventive step as set out for claim 1 of the main request in section 3 above also applies, without any modification, to claim 1 of each of auxiliary requests 2 to 8.

Conclusion

4.5 As a consequence, the subject-matter of claim 1 of each of auxiliary requests 1 to 8 does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated