Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 10 December 2024

Case Number: T 2140/22 - 3.3.04

Application Number: 17794903.9

Publication Number: 3528847

IPC: A61K31/197, A61K47/10, A61J1/00, A61K9/00, A61K9/06, A61K31/00

Language of the proceedings: EN

Title of invention:
High-stability packaged solutions of T4 thyroid hormone

Patent Proprietor:
Altergon SA

Opponent:
Uni-Pharma Kleon Tsetis
Pharmaceutical Laboratories S.A.

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12, 13

Keyword:
Inventive step - (no)
Auxiliary request - admittance (no)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 2140/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 December 2024

Appellant: (Opponent)	Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A. 14th Km, National Road 1 145 64 Kifissia (GR)
Representative:	Sonnenhauser, Thomas Martin Wuesthoff & Wuesthoff Patentanwälte und Rechtsanwalt PartG mbB Schweigerstraße 2 81541 München (DE)
Respondent: (Patent Proprietor)	Altergon SA Via Dogana Vecchia 2 6901 Lugano (CH)
Representative:	M. Zardi & Co S.A. Via G. B. Pioda, 6 6900 Lugano (CH)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 July 2022 rejecting the opposition filed against European patent No. 3528847 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	J.-M. Schwaller
Members:	R. Hauss
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 528 847 (the patent in suit) was granted with a set of twelve claims. Claim 1 reads as follows:

1. A pharmaceutical preparation of T4 thyroid hormone, in ready-to-use packaging, consisting of a container pre-filled with an alcohol-free water-glycerol solution of hormone T4, said container being a one-component LDPE plastic container, placed in a sealed sachet consisting of laminated films made of polyethylene, aluminium and polyethylene terephthalate.

II. The patent in suit was opposed under Article 100(a), (b) and (c) EPC.

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

D1: Amdipharm Mercury Company Limited, "Eltroxin 100 micrograms per 5 ml oral solution" SPC, 04/09/2013

D2: WO 2013/072304 A1

D14: Wikipedia entry: "Thyroid hormones" (undated, filed by the appellant by letter of 24/11/2021)

D17: Three-month stability studies, 07/06/2022

IV. The decision under appeal is the opposition division's decision ruling that none of the grounds for opposition under Articles 100(a), (b) and (c) EPC prejudiced the maintenance of the patent as granted and rejecting the opposition.

V. In the decision under appeal, inventive step was assessed starting from the disclosure of D1 and, in a second approach, D2. With either approach, the claimed subject-matter was held to involve an inventive step.

Starting from the disclosure of D1, the objective technical problem was to provide an alternative pharmaceutical preparation of T4 thyroid hormone in ready-to-use packaging. The solution of replacing the multi-dose containers (amber (Type III) glass bottles) disclosed in D1 with the claimed LDPE+PET/Al/PE packaging would not have been obvious in view of the cited prior art. This was because the disclosure of single-dose LDPE containers in sachets in document D2 was not compatible with the teaching of D1, where a multi-dose bottle was used.

Starting from the disclosure of LDPE+PET/Al/PE packaging in D2 and based on the data provided in Example 3 of the opposed patent, the objective technical problem was to improve the long-term stability of T4 solutions stored in LDPE+PET/Al/PE packaging. The cited prior art and common general knowledge would not have given the skilled person an incentive to consider alcohol-free solutions of T4 in water/glycerol.

VI. The opponent (appellant) filed an appeal against this decision, pursuing objections on the issues of insufficiency of disclosure and lack of inventive step starting from the disclosure of D1.

VII. With its reply to the appeal, the patent proprietor (respondent) filed an amended set of claims as "auxiliary request 1". Claim 1 of auxiliary request 1 is identical to claim 1 as granted, except that it additionally specifies that the preparation is in

single-dose form, containing 5 to 350 µg T4 thyroid hormone.

VIII. In a further written submission, the appellant pointed out that auxiliary request 1 had not been substantiated and that no reason had been provided as to why this request had not been filed before the department of first instance. Moreover, it was not apparent that this new claim request could overcome any of the objections.

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 made, *inter alia*, the following points:

(a) In accordance with the appellant's objection, inventive step would be assessed starting from the disclosure of document D1.

(b) The objective technical problem could be formulated as the provision of an alternative pharmaceutical preparation that provided the T4 solution in suitable alternative packaging.

(c) On this basis, the board was of the view that the subject-matter of claim 1 as granted did not involve an inventive step.

(d) With regard to auxiliary request 1, the respondent had not provided any substantiation as to why this request might overcome any of the objections raised, why it was not filed in the proceedings before the opposition division or why the circumstances of the appeal case might justify its admittance. It was thus to be expected that auxiliary request 1 would not be admitted.

X. Oral proceedings before the board took place on 10 December 2024. The debate addressed the issues of whether the main request involved an inventive step and whether auxiliary request 1 should be admitted.

XI. The appellant's relevant arguments can be summarised as follows.

Inventive step - main request

The product according to claim 1 as granted differed from the product disclosed in D1 only by its packaging. The appellant agreed with the objective technical problem as formulated by the board in its communication under Article 15(1) RPBA, namely, the provision of an alternative pharmaceutical preparation that provided the T4 solution in suitable alternative packaging.

The respondent's line of argument relying on a different formulation of the objective technical problem which included the aspect of high protection against T4/T3 conversion had been presented for the first time at the oral proceedings before the board, and should not be admitted.

Within the framework of the problem-and-solution approach, it would in any case not be warranted to include high protection against T4/T3 conversion in the formulation of the objective technical problem, since this technical effect had not been shown by comparison with the product of D1. In this context, it should be kept in mind that the patent in suit attributed the observed stability against T4/T3 conversion to the fact that the claimed T4 solutions did not contain ethanol. This, however, was not a distinguishing feature over the product of D1.

The person skilled in the art seeking to solve the objective technical problem of providing alternative

packaging would have found a solution in document D2, which disclosed LDPE containers in PET/Al/PE sachets as a suitable packaging option for similar T4 solutions.

D2 also disclosed that T4 solutions stored in this packaging system had good storage stability, including with regard to T4/T3 conversion, if that aspect of stability were to be taken into account.

Admittance - auxiliary request 1

The appellant had used document D1 as the starting point for assessing inventive step in its notice of opposition. Contrary to the respondent's argument, auxiliary request 1 was thus not presented in response to a new aspect introduced by the opposition division.

When it filed auxiliary request 1 with its reply to the appeal, the respondent had not provided any substantiation as to the timing and rationale for this request. It was not self-evident how this request could overcome any of the objections raised in the proceedings. The appellant had pointed out this lack of substantiation in a letter submitted two months after the reply to the appeal was filed and more than one and a half years before the appeal oral proceedings took place, without any reaction from the respondent. Learning only during the oral proceedings before the board in what way the respondent intended to use auxiliary request 1 to establish an inventive step did not leave the appellant adequate time to react.

XII. The respondent's relevant arguments can be summarised as follows.

Inventive step - main request

It was not correct to use D1 as the starting point for the assessment of inventive step because document D2

was in fact the closest prior art. Any conclusion on inventive step reached on the basis of D1 as the starting point would, therefore, not be meaningful.

If D1 were nevertheless to be used as the starting point, the following analysis applied.

It was acknowledged that the product of claim 1 as granted differed only by its packaging from the product disclosed in D1.

The experimental data reported in the patent in suit showed that, in terms of storage stability, the claimed product provided high protection against unwanted premature conversion of T4 to T3 (see Example 3).

Reference was also made to the appellant's experimental data provided in D17; specifically, the comparison presented in Table 2 of D17 for sample D22-02#2 (a T4 solution according to claim 1). This showed T3 concentrations of 4.60% after three months' storage in an amber glass bottle at 40°C ± 2°C and 75% RH ± 5%, vs. 3.14% after three months' storage in LDPE+PET/Al/PE packaging under the same accelerated conditions.

The shelf life of 18 months indicated in D1 merely related to unspecified impurities in general, whereas the active metabolite T3 would not be considered an impurity. Thus, D1 did not provide any information about the stability of its product against T4/T3 conversion and there was no evidence that this effect was inherently attained by the product of D1.

To reflect the claimed product's actual contribution to the art, the objective technical problem should be formulated as being the provision of a product (including both solution and packaging) which is highly protective against the conversion of T4 to T3.

If the objective technical problem were to focus, instead, on a change in packaging, this would constitute *ex post facto* reasoning, since the person skilled in the art was not selectively guided to work only on the packaging.

As to obviousness, the person skilled in the art would in any case have had reservations about changing the packaging of a successful product with regulatory and marketing approval, such as the product of D1. Furthermore, it had to be assumed that the packaging in D1 was critical to product stability. The skilled person would not have had the expectation that any type of packaging, and specifically the packaging system defined in claim 1 as granted, would be equally suitable and, moreover, would ensure high protection against the conversion of T4 to T3.

D1 itself did not address the issue of T4/T3 conversion, nor did it suggest any change to the packaging.

In document D2, the packaging option of using LDPE containers in a sachet was not disclosed in the context of avoiding T4/T3 conversion during storage. Rather, this system was proposed for entirely unrelated reasons, namely to provide squeezable single-dose containers and for protection against solvent (ethanol) evaporation. The packaging system disclosed in D2 was not known in the art as a conventional system, and it would not have been chosen for similarity to the system in D1, either.

The skilled person would have had no reason to pick specifically the system using LDPE bottles placed in a PET/Al/PE sachet from all the options disclosed in the prior art, or even from the options described

in D2, in order to solve the objective technical problem.

Admittance - auxiliary request 1

Auxiliary request 1 was filed in response to the opposition division's assessment of inventive step starting from the disclosure of D1 set out in the decision under appeal.

The amendments were straightforward and predictable in that they further limited the claimed scope in accordance with the features of dependent claim 6 and provided further delimitation over D1.

The respondent had not filed this request as a fallback position during the proceedings at first instance because it had been confident that D1 would be discarded as a potential starting point for the assessment of inventive step in view of the opposition division's preliminary written opinion stating that D2 was considered the closest prior art.

XIII. The parties' final requests were as follows:

- The appellant requested that the decision under appeal be set aside and that the patent be revoked. It also requested that auxiliary request 1 not be admitted.

- The respondent requested that the appeal be dismissed and that the patent be maintained as granted or, as an auxiliary measure, that the patent be maintained in amended form on the basis of the claims of auxiliary request 1 as filed with its reply to the grounds of appeal.

Reasons for the Decision

1. Inventive step (Articles 52(1) and 56 EPC)

Patent in suit

1.1 The patent in suit (see paragraphs [0001] and [0010]) relates to pharmaceutical preparations of thyroid hormones and aims to provide shelf-stable pharmaceutical products containing solutions of T4 thyroid hormone (i.e. tetraiodothyronine or thyroxine) characterised by high physical, chemical and microbiological stability.

1.2 Avoiding unwanted premature conversion of T4 into the active metabolite T3 (triiodothyronine or liothyronine) is mentioned as a relevant aspect of chemical stability. As set out in the patent in suit (see paragraphs [0009] and [0022]), although T4 is converted into T3 in the body after administration, premature T4/T3 conversion during storage may cause inaccuracy of the hormone dose administered, due to the different pharmacokinetics and higher potency of T3. The concern with this is over-dosing, if premature T4/T3 conversion were to occur at significant levels. A need is identified for packaged T4 solutions which remain shelf-stable, particularly over the medium/long term, i.e. for 12/18 months, at room temperature (see paragraph [0010] of the patent in suit).

1.3 Claim 1 as granted is directed to a pharmaceutical preparation containing an alcohol-free water-glycerol solution of T4 in a one-component LDPE plastic container that is placed in a sealed sachet consisting of laminated films made of polyethylene terephthalate, aluminium and polyethylene (LDPE+PET/Al/PE system).

1.4 Paragraph [0012] of the patent defines "alcohol" as alkanol with a molecular weight lower than 80 daltons, which does not include glycerol (92.1 Da).

1.5 The patent in suit sets out that alcohol (ethanol) was used in water/alcohol/glycerol-type solutions according to the prior art in order to enhance the solubility of T4. The inventors found that stability against premature T4/T3 conversion was improved if alcohol was omitted from the solutions (see paragraphs [0010] and [0011] of the patent in suit).

Starting point for the assessment of inventive step

1.6 The respondent contended that document D2 was the closest prior art. Therefore, only D2 should be considered as the starting point for the assessment of inventive step. The case law of the boards of appeal considering any potential starting point in the prior art was not correct, and in the case at hand it was not correct to select D1 as the starting point.

1.7 The board notes, however, that neither the opposition division in the decision under appeal nor the appellant in its appeal submissions argued that the claimed subject-matter lacked an inventive step starting from the disclosure of document D2.

The appellant's arguments on inventive step as set out in its appeal submissions were exclusively based on an approach starting from the disclosure of document D1 and taking document D2 into account as a supplementary disclosure. Thus, the appellant essentially argued that the opposition division had been wrong to find the subject-matter of claim 1 inventive starting from the disclosure of D1.

1.8 The board, accordingly, assessed inventive step starting from the disclosure of D1 in order to take account of the appellant's actual objection.

1.9 The respondent's argument that D1 is not a permissible starting point for assessing inventive step because another document is the "closest" prior art is flawed since it is based on a misconception regarding the role of the so-called "closest prior art" in the application of the problem-and-solution approach. The following considerations apply.

1.9.1 Article 56 EPC provides that an invention (i.e. the claimed subject-matter under consideration) involves 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 here is any prior disclosure that is eligible under Article 56 EPC, i.e the entire state of the art as defined in Article 54(2) EPC, without any ranking or distinction.

Any such prior disclosure may be used as the starting point for the assessment of inventive step, and also as supplementary prior art in alternative scenarios with different starting points.

It is the established case law of the boards of appeal, based on the wording of Article 56 EPC, that if inventive step is to be acknowledged, the claimed subject-matter must be inventive starting from any starting point in the prior art. If inventive step is to be denied, the choice of starting point needs no specific justification (see also "Case Law of the Boards of Appeal of the European Patent Office", 10th ed., 2022, I.D.3.1).

1.9.2 The selection of a starting point serves the purpose of assessing inventive step and is performed by the

body deciding on inventive step, which makes its selection from the cited prior-art disclosures that are eligible under Article 56 EPC. Depending on the circumstances of the individual case, either only one starting point or several alternative starting points will have to be considered.

1.9.3 In the case at hand, the only line of argument presented by the appellant in the appeal proceedings with regard to a lack of inventive step is based on an approach using the disclosure of D1 as the starting point. In this situation, no selection between different potential starting points is required. The only starting point to be considered by the board for the purpose of examining the merit of the appellant's inventive step objection is D1.

1.9.4 The practice of selecting, in cases where this is appropriate, one among several potential starting points on the basis of its greater similarity to the claimed subject-matter and its intended purpose (the so-called closest prior art) serves efficiency by permitting a combined assessment.

The test is to establish if the claimed subject-matter would have been non-obvious even when starting from such a particularly "promising" starting point. Thus, in a situation where inventive step is ultimately to be acknowledged, carrying out a detailed assessment of inventive step according to the problem-and-solution approach with the closest prior art as the starting point may avoid having to perform an equally detailed assessment also for numerous alternative starting points that are comparatively more remote.

The consideration in such a case is that since an inventive step can be acknowledged in a scenario starting from the closest prior art, it can also be

acknowledged, for at least the same reasons, starting from the more remote alternative starting points, without the need for a detailed analysis in each of these cases.

Obviously, this shortcut only works in cases where it can be confirmed that the same reasons for acknowledging an inventive step are indeed also applicable to the scenarios based on the alternative starting points. The reasoning addressing the alternative scenarios must at least set out why this criterion is met.

Nonetheless, comparative remoteness does not prohibit the consideration of any prior disclosure as a starting point in a detailed step-by-step assessment according to the problem-and-solution approach. If a chosen starting point is "too remote" from the claimed subject-matter in terms of structural features and purpose, the problem-and-solution approach will simply not result in a finding of obviousness.

1.9.5 In view of its purpose as described above, the concept of the "closest prior art" is not relevant in a situation where an inventive step cannot ultimately be acknowledged (see point 1.9.1 above, last sentence). If the assessment of inventive step from a given starting point results in a finding of obviousness, this starting point is evidently close enough to the claimed invention to lead to a conclusion that decides the question of inventive step.

1.9.6 Since, in the case at hand, the assessment with D1 as the starting point resulted in a finding of obviousness (as set out below), it is not relevant whether another piece of prior art might be even closer to the claimed subject-matter.

For the sake of completeness, the board also notes that it would not make sense in any case to attempt to rank documents D1 and D2 in terms of which document might be considered "closest" to the claimed subject-matter.

In terms of purpose, both documents provide information on the storage stability of T4 solutions.

The technical features distinguishing the claimed product from that of D1 concern the packaging. D2, on the other hand, discloses T4 solutions comprising ethanol, while the packaging is identical to that in claim 1 as granted. Thus, the only technical feature distinguishing the claimed product from the disclosure of D2 is the requirement that the T4 solution be "alcohol-free".

The objective technical problems derived from these technical differences (see point 1.12 below) would differ, giving rise to two separate scenarios.

It is, therefore, meaningless to assert that D2 is "closer" to the claimed invention than D1, or *vice versa*. Assessing inventive step starting from the disclosure of D2 (as advocated by the respondent) would not permit any conclusion to be drawn on the merit of the appellant's independent approach that starts from the disclosure of D1 and considers different distinguishing technical features and a different objective technical problem.

1.10 D1 is an SPC (Summary of Product Characteristics) of "*Eltroxin 100 micrograms per 5 ml oral solution*", i.e. a medicament of the prior art that had received regulatory approval and marketing authorisation. The solution described in D1 is alcohol-free (within the meaning given to this term in the patent in suit, see point 1.4 above) and is composed of levothyroxine sodium (100 µg/5 ml), glycerol (3,780 mg/5 ml), sodium

methyl parahydroxybenzoate, citric acid, sodium hydroxide and water (see D1: points 1, 2 and 6.1). It is provided in a 100 ml amber (Type III) glass bottle. The 5 ml dose is supposed to be retrieved with the help of a 5 ml oral medication syringe or a plastic double-ended 2.5/5 ml spoon provided with the bottle (see D1: point 6.5). The shelf life is indicated as being 18 months (unopened), or eight weeks after opening (see D1: point 6.3).

Criteria for the avoidance of hindsight

1.11 In the application of the problem-and-solution approach, the following requirements relating to the formulation of the technical problem and the assessment of the obviousness of its solution ensure that inventive step is assessed without hindsight.

- The technical problem is determined objectively and must not contain elements of the solution.

- The question:

  "What teaching would the skilled person seeking to solve the objective technical problem have derived from the disclosure providing the starting point in combination with any supplementary prior-art disclosures?"

  must be answered from the skilled person's point of view before the effective date.

Objective technical problem and solution

1.12 According to the first of these requirements, the technical problem is determined objectively, namely on the basis of a technical effect that is associated with a technical feature distinguishing the claimed

subject-matter from the disclosure of the starting point in the prior art.

1.13 The T4 solution described in D1 conforms to the definition of the solution in claim 1 as granted. It was thus not in dispute that the pharmaceutical preparation of claim 1 differs from that disclosed in D1 only by the packaging, i.e. the LDPE+PET/Al/PE system according to claim 1 at issue versus the 100 ml amber (Type III) multi-dose glass bottle disclosed in D1.

1.14 The immediately apparent technical effect of this difference is that the same T4 solution is presented in different packaging. The appellant did not contest that the claimed product provides acceptable long-term stability of the packaged solution. Thus, the claimed product is an alternative to that of D1 in the sense that its shelf life is adequate, as is the shelf life of 18 months reported in D1.

1.15 As a consequence of the considerations in points 1.13 and 1.14 relating to the distinguishing technical feature(s) and associated technical effects, the objective technical problem is to provide an alternative pharmaceutical preparation that provides the T4 solution in suitable alternative packaging.

1.16 The respondent objected to this formulation of the objective technical problem on two accounts.

1.16.1 Firstly, the respondent contended that the formulation of the objective technical problem should include the technical effect of providing "high" stability against premature T4/T3 conversion, which had been demonstrated for the claimed preparations in Example 3 of the patent in suit. The respondent also referred to experimental data originally provided by the appellant in D17 as

arguably showing even superior stability in comparison with the packaging option disclosed in D1.

1.16.2 Secondly, the respondent argued that focusing the technical problem on a change in packaging introduced hindsight by including an element of the solution into the formulation of the technical problem.

1.17 The board finds neither of these arguments persuasive, for the reasons given below. The first argument is addressed in section 1.18. The second argument is addressed in section 1.19.

1.18 The following considerations apply regarding the technical effects of stability against T4/T3 conversion and shelf life in general.

1.18.1 The patent in suit sets out that the overall stability of the T4 preparations according to the patent, in terms of T4 potency, total impurities and microbial contaminations, was found acceptable for pharmaceutical use in every aspect (see paragraph [0026] of the patent specification, in view of paragraph [0010]). The appellant did not contest this.

1.18.2 Furthermore, the comparative tests shown in Example 3 demonstrate long-term stability against T4/T3 conversion for preparations as defined in claim 1. However, no comparison with the preparation disclosed in D1 is provided. The following passages are relevant in this context.

- According to paragraphs [0010] and [0026], the packaged T4 solutions according to the patent in suit are more stable against unwanted premature conversion of T4 to T3 than prior-art solutions containing alcohol, such as those disclosed in document D2. Moreover, the formulations cannot

suffer from accidental reduction of their alcohol content by evaporation since they do not contain any volatile alcohol. Thus, unwanted variations in hormone solubility or stability are avoided, which ensures that the amount of administered hormone will be better reproducible.

All these statements relate to advantages attained in comparison with T4 solutions containing alcohol rather than in comparison with the product of D1.

- Stability against T4/T3 conversion over 18 months, with an acceptance limit of 2.5% conversion, is shown in Example 3 of the patent in suit for a number of packaged T4 solutions conforming to claim 1 and having concentrations of T4 ranging from 25 to 100 µg/ml (solutions prepared according to Example 2, packaged in an LDPE+PET/Al/PE system). The comparative samples tested were formulations containing alcohol and packaged in an LDPE+PET/Al/PE system (see Example 1).

Thus, the comparative tests of Example 3 do not represent a comparison with the product according to D1, which contains no alcohol and is packaged in glass bottles. The patent in suit does not provide any comparative stability data comparing the amber glass bottles of D1 with LDPE+PET/Al/PE packaging.

1.18.3 In relation to the alleged technical effect of high protection against T4/T3 conversion, the respondent also referred to the comparative test presented in Table 2 of D17 for sample D22-02#2 (Levothyroxine sodium at 100 µg/ml in glycerol 85% i.e. a T4 solution according to claim 1). The initial T3 concentration in this sample ("Time Point: t=0") is indicated as being 0.29%. The T3 concentration after three months' storage at 40°C ± 2°C and 75% RH ± 5% in an amber glass

bottle is reported as being 4.60%. The T3 concentration after three months' storage under the same accelerated conditions in an LDPE bottle placed in a PET/Al/PE sachet is reported as being 3.14%.

The respondent's argument that the comparative data presented for sample D22-02#2 in Table 2 of D17 might be indicative of the claimed product having superior stability against T4/T3 conversion is not consistent with the formulation of the objective technical problem proposed by the respondent, which refers to "high" rather than "improved" protection.

Furthermore, this argument is new. The opposition division considered that the data in D17 showed that both types of packaging provided comparable stability (see the decision under appeal, Reasons 11.2.1.2), and the respondent did not object to this conclusion in its reply to the grounds of appeal. The respondent's reference to D17 as showing superior stability was presented for the first time at the oral proceedings before the board.

Irrespective of the question of admittance, the board in any case takes the view that the data in D17 cannot be regarded as conclusive evidence in the respondent's favour, for the following reasons.

The respondent relied on a single data point, namely the results reported in Table 2 for sample D22-02#2. No indication about statistical significance is given in D17. It cannot be inferred from the available information that more than one sample of each formulation per packaging type was tested.

With both types of packaging, the T4 concentration was diminished to below 94% of the initial concentration, with a substantial content of total impurities. It is not clear how the data observed after three

months under the described accelerated storage conditions (40°C ± 2°C and 75% RH ± 5%) relate to stability after defined periods at room temperature and lower humidity. Moreover, in the case of sample D22-01#4 (100 µg/ml in 50% glycerol), the results seem to have been reversed, i.e. the solution in the glass bottle turned out to be more stable in all aspects tested; however, significant deterioration of T4 occurred in both types of packaging. Under these circumstances, the single data point in D17 cited by the respondent (i.e. the results for sample D22-02#2) cannot be considered conclusive as to whether one of the two packaging options tested achieves better protection against T4/T3 conversion, and for what duration, under usual storage conditions.

1.18.4 The prior art D1 specifies a shelf life of 18 months. While D1 does not mention the issue of premature T4/T3 conversion, the following considerations apply.

The respondent failed to substantiate its assertion that the shelf life indicated in D1 was established exclusively on the basis of the parameter "total impurities" and that this excluded any consideration of T3. This view is based on speculation and is not deemed to be correct either, for the following reasons.

D1 presents a value for shelf life but not for total impurities. "Shelf life" indicates a time period during which a medicament, if stored correctly, is expected to comply with its specifications and remain sufficiently stable to be safe for use. This period is established on the basis of experimental data.

Considering its purpose, the shelf life must take all potential safety risks into account. This includes the reduction over time of the concentration of the active agent, which is always taken into account in the

assessment of storage stability. In the present case, this is the reduction of the concentration of T4.

T3, being a different chemical species, would not just have been considered to be interchangeable with the active agent T4 in view of its known different pharmacokinetics and higher potency. In the context of D1, T3 is not the active agent, whether formally categorised as forming part of the "total impurities" or not.

This consideration is not changed by the fact that T3 may be included as an active agent in other medicaments. The respondent mentioned, with reference to document D14, that combination products containing synthetic T3/T4 combinations in different ratios as the active agent were known in the art. However, in such products, the different properties and potencies of T3 and T4 would have been factored in for product strength, and the products would be required to maintain stable concentrations of both T4 and T3 during their shelf lives. In other words, it would not simply be assumed that a stable therapeutic performance over time could be achieved, irrespective of uncontrolled T4/T3 conversion. Moreover, such products are typically marketed as in solid form as tablets. D14 does not mention whether any of these combination products were presented in the form of (typically less stable) solutions or whether there were concerns about premature T4/T3 conversion.

Returning to the T4 solution disclosed in D1, if there was a concern of overdosing (and thus toxicity) due to premature conversion of T4 to T3 (see point 1.2 above), this would have had to be taken into account when the shelf life of the product of D1 was established.

Thus, as the shelf life of 18 months indicated in D1 relates to overall safety, and no concerns are mentioned in relation to T4/T3 conversion, the board has no reason to assume that the stability of the product of D1 over 18 months was inadequate, including in relation to premature T4/T3 conversion.

1.18.5 In summary, it is not shown in the patent in suit or by the post-filed data (D17) relied on by the respondent that the claimed product provides improved stability against T4/T3 conversion in comparison to the product of D1, which differs from the claimed product only by its packaging. Comparing the information in the patent in suit and in D1 in light of common general knowledge, the upshot is that it can be acknowledged that both the product of D1 and the product according to claim 1 as granted provide adequate long-term general stability, which includes in both cases the aspect of stability against premature T4/T3 conversion.

1.18.6 This technical effect is reflected in the board's formulation of the objective technical problem (see point 1.15 above) by the requirement that an "alternative" pharmaceutical preparation is to be provided. This alternative preparation is a packaged T4 solution which, like the product of D1, provides adequate stability.

1.19 As discussed above, a further requirement is that providing the alternative preparation involves providing the same T4 solution in alternative packaging. The board is of the view that it is indeed correct to include the aim of providing the T4 solution in suitable alternative packaging in the formulation of the objective technical problem (see points 1.14

and 1.19.1) and that this formulation does not introduce hindsight (see point 1.19.2).

1.19.1 Leaving the technical problem completely open for any modification of the product of D1 would not be appropriate since this would also cover the option of modifying the T4 solution but not the packaging. This would not be a suitable technical measure for achieving the technical effect established in comparison with D1, namely that the same solution is presented in a different packaging. The objective technical problem should, however, be based on the identified technical effect.

1.19.2 The formulation of the objective technical problem as set out in point 1.15 above does not introduce hindsight since it remains on a sufficiently general level so as not to anticipate any element of the solution. The actual solution to the technical problem is provided by the specific combination of technical features that characterise the modified packaging, namely a one-component LDPE plastic container placed in a sealed sachet consisting of laminated films made of polyethylene, aluminium and polyethylene terephthalate. These features are not anticipated or suggested in the objective technical problem as formulated by the board.

Obviousness of the solution

1.20 What has to be established in this last step of the problem-and-solution approach is whether the person skilled in the art would have considered the technical features of the LDPE+PET/Al/PE packaging defined in claim 1 to be an obvious solution to the technical problem of providing an alternative preparation (i.e. one with adequate long-term stability) by providing the same T4 solution in different suitable packaging.

1.21 The board sees no merit in the respondent's argument that the person skilled in the art would *a priori* not have considered modifying the packaging, as this is precisely the objective technical problem that the skilled person is tasked with in the scenario under consideration.

1.22 As an additional observation, leaving the technical problem open for any modification of the prior art product, as suggested by the respondent, could not have provided a basis for establishing an inventive step either. Even if the more general technical problem of providing an alternative product were to be considered, modifying the packaging would have been one of two obvious general routes for solving it since it would have been evident to the skilled person that either the T4 solution or its packaging could be modified to provide an alternative product. Moreover, providing the same T4 solution in inert alternative packaging would have been considered a likely option for maintaining stability at the same level.

1.23 Contrary to the respondent's further argument, it is not uncommon that the packaging of an existing medicament may be modified, e.g. by changing the volume or the material of a container. Many reasons can be imagined for doing so, e.g. for more convenient dosing or for avoiding glass breakage.

1.24 At the oral proceedings before the board, the respondent conceded that the person skilled in the art might well have considered modifying the packaging. The criterion that was crucial for obviousness, however, was the skilled person's expectation of success. According to the respondent, the skilled person would not have consulted document D2, nor would they have expected the packaging according to claim 1

to provide a solution to the objective technical problem.

1.25 The board agrees that expectation of success is relevant, but its conclusions differ from those suggested by the respondent, as set out below.

1.26 The board is of the view that the person skilled in the art seeking to solve the objective technical problem would have consulted D2 since it relates to the same type of medicament (T4 solutions) and describes possible packaging options under the aspect of product stability.

1.27 D2 discloses oral pharmaceutical solutions of T4 that contain ethanol as a solvent component in addition to glycerol (see e.g. D2: Example 1), *inter alia* in single-dose packaging that is in conformity with claim 1 of the main request (see D2: Examples 2.D and 3). In relation to this embodiment, D2 reports favourable data for the concentrations of T4, T3 and total impurities excluding T3, observed at various points in time during accelerated stability testing at 30°C/65% RH (see Table 9, last line and Table 10, first line). Similar results were seen with industrial batches, including in 18-month stability testing at 25°C/60% RH (see D2: page 19, lines 2 to 4 and Tables 11 to 14).

1.28 As the T4 solutions according to claim 1 as granted do not contain ethanol, the additional finding reported in D2 that evaporation of ethanol is prevented by the proposed LDPE+PET/Al/PE packaging system is irrelevant to the case at hand.

1.29 The question to be answered is whether the person skilled in the art seeking to solve the objective technical problem would have had the expectation that

the LDPE+PET/Al/PE packaging option disclosed in document D2 would be suitable as an alternative packaging option for the pharmaceutical solution disclosed in D1, without having a detrimental effect on product properties such as shelf life (including protection against T4/T3 conversion).

1.30 Due to the formulation of the objective technical problem as the provision of an alternative, the mere fact that D2 and other prior-art documents disclose other types of packaging besides the LDPE+PET/Al/PE system does not make the selection of this particular system inventive, in the absence of a technical prejudice or other dissuading argument against it.

1.31 No convincing reason was presented as to why the person skilled in the art would have been dissuaded from considering the packaging system according to D2 as an alternative option to the multi-dose amber glass bottles disclosed in D1.

1.32 In particular, the person skilled in the art had no specific reason to assume that the T4 solution of D1, which was already known to be stable with a shelf life of 18 months in a glass bottle, would be less stable when packaged in the LDPE+PET/Al/PE system disclosed in D2. The similar T4 solutions described in D2 had been shown to be stable in this packaging system, including with regard to their stability against T4/T3 conversion (see point 1.27 above). As there was no indication that this good stability was in any way linked to the presence of ethanol, the person skilled in the art would have expected that the LDPE+PET/Al/PE packaging system would work as well for the ethanol-free T4 solution of D1, without a negative impact on stability.

1.33 It does not follow from the respondent's argument that the LDPE+PET/Al/PE system was not a conventionally used standard packaging system that this alone would have dissuaded the skilled person from using it.

1.34 Contrary to what was asserted by the opposition division (see the decision under appeal, Reasons 11.2.3) and by the respondent, there is also no requirement derivable from the objective technical problem that the alternative packaging must be "compatible" with the packaging system disclosed in D1, in the sense that it would have to provide another multi-dose container. The new packaging is, after all, supposed to be an alternative. What it has to do is allow dosing of the T4 solution and ensure an adequate shelf life.

If anything, a transition to single-dose containers as disclosed in D2 would have been considered advantageous for stability because in such containers, the whole of the solution remains protected against the environment until the moment the container is opened and the solution is administered. In contrast, with the multi-dose bottles according to D1, intermittent contact of the solution with the environment is unavoidable each time another dose is withdrawn from the bottle.

1.35 It follows from the above considerations that the use of the packaging system known from D2 that corresponds to the definition in claim 1 as granted would have appeared obvious to the skilled person faced with the objective technical problem.

1.36 As a consequence, the subject-matter of claim 1 as granted lacks an inventive step within the meaning of Article 56 EPC.

2. Admittance of auxiliary request 1

2.1 Auxiliary request 1 was filed for the first time with the respondent's reply to the statement setting out the grounds of appeal, and thus it constitutes an amendment to the respondent's case according to Article 12(4) RPBA, the admittance of which is subject to the board's discretion.

2.2 The accompanying letter merely indicated (see point 2: "Enclosures") that the amendment incorporated the features of claim 6 into claim 1.

This brief explanation cannot be considered to meet the requirements of Article 12(3),(4), second paragraph, and (6), second paragraph, RPBA, particularly because no substantiation was provided as to

(a) why this request was believed to overcome any of the objections raised;

(b) why it had not been filed in the proceedings before the opposition division and/or why the circumstances of the appeal proceedings might justify its admittance.

2.3 According to the established case law of the boards, unsubstantiated auxiliary requests cannot be considered or are not admissible in appeal proceedings if the amendments made are not self-explanatory (see "Case Law of the Boards of Appeal of the European Patent Office", 10th ed. 2022, V.A.5.12.6). In the present case, it is not self-explanatory how the amendment by incorporation of the features of claim 6 into claim 1, i.e. the restriction to a single-dose form containing 5 to 350 µg T4, could overcome the inventive step objection against the main request. The dosage range for a single dose is in any case not a distinguishing feature over

the disclosure of D1 (points 1, 2: "5 ml dose" and 4.2), and single-dose packaging is disclosed in D2.

2.4 Even after both the appellant and the board pointed out the lack of substantiation (see points VIII. and IX.(d) above), the respondent did not reply in writing but instead waited until the day of the oral proceedings to present its arguments in relation to auxiliary request 1.

2.5 The respondent submitted, in particular, that auxiliary request 1 had been presented in response to the opposition division's unexpected reasoning that considered D1 as a possible starting point for assessing inventive step, and that the amendments were straightforward as they further restricted the claimed scope in comparison with the main request.

2.6 In the board's view, these arguments are inadequate to support a case for the admittance of auxiliary request 1, for the following reasons.

2.6.1 In its written preliminary opinion, the opposition division stated that it regarded D2 as the "closest" prior art, but also briefly outlined its inventive step approach starting from D1 (see point 9.3.1 of the annex of the summons to oral proceedings). Even if it were to be considered that the decision under appeal deviated from the preliminary opinion by providing a more detailed assessment of inventive step starting from D1, the respondent was not exonerated by the mere filing of amended claims from the obligation of expressly specifying the relevance of the amendments for overcoming the inventive step objection raised by the opponent.

2.6.2 In any case, since D1 was used by the appellant as a starting point for the assessment of inventive step from the very start of the opposition proceedings (see the notice of opposition, section 3.1), the respondent should have presented any auxiliary request aiming to improve its position with regard to this line of argument in the proceedings before the opposition division.

2.6.3 In *inter partes* proceedings such as opposition proceedings, a party has to anticipate and prepare for the eventuality that the opposition division might agree with the arguments of the opposing party. Also, a preliminary opinion provided by an opposition division is not binding as regards the final decision.

2.6.4 As set out in point 2.3 above, the amendments in auxiliary request 1 are not straightforward in the sense of being self-explanatory.

2.7 As an additional observation, the board also fails to see how the circumstances of the appeal case could have justified the admittance of auxiliary request 1.

2.8 Since the requirements of Article 12(3) and (4) RPBA are not met, the board decided not to admit auxiliary request 1 (Articles 12(3) and 12(5) RPBA).

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:

I. Aperribay J.-M. Schwaller

Decision electronically authenticated