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Title of invention:
Pharmaceutical compositions for the treatment of Helicobacter pylori associated diseases

Applicant:
Al-Mehdar, Abo Bakr Mohammed Ali

Headword:
Pharmaceutical compositions for the treatment of Helicobacter pylori associated diseases/Al-Mehdar, Abo Bakr Mohammed Ali

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(3)

Keyword:
Main request and auxiliary requests I to IV - Inventive step (no)
Auxiliary request V - Admission into the appeal proceedings (no)

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Case Number: T 1823/17 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 February 2020

Appellant: (Applicant)	Al-Mehdar, Abo Bakr Mohammed Ali King Abdulaziz Street Riyadh (SA)
Representative:	Kröncke, Rolf Gramm, Lins & Partner Patent- und Rechtsanwälte PartGmbB Freundallee 13 a 30173 Hannover (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 13 March 2017 refusing European patent application No. 12008098.1 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application n° 12 008 098.1. The decision was based on 2 sets of claims filed as main request with letter of 13 May 2016 and as auxiliary request 1 with letter of 22 December 2016.

Claim 1 of the main request read as follows:

"1. An oral pharmaceutical composition for treatment of Helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally at least one agent selected from the group consisting of taurolidine or taurultam or a combination thereof, a zinc amino acid chelate, tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the substance or substances selected from taurolidine or taurultam or a combination thereof, the zinc amino acid chelate, the tromethamole is/are comprised in the outer layer of fast release phase."

The subject-matter of claim 1 of auxiliary request 1 was further specified by the following feature **"and the outer layer comprises the antibiotic or mixture of antibiotics"**.

II. The documents cited during the examination and appeal proceedings included the following:
D1: US 2004/082514
D4: Suzuki Hidekazu et al., Gastroenterology, Vol. 120, no 5 Supplement 1, April 2001 (2001-04), page A.650
D10: US 6 555 534
D11: WO 2007/070164

III. According to the decision under appeal, the closest prior art was considered to be document D1, as it disclosed a biphasic tablet comprising enteric coated omeprazole in the core (i.e. inner slow release layer) and the antibiotic pentagastrin (PG) in an immediate release-type coating layer (i.e. outer fast release layer). The subject-matter of claim 1 differed from D1 in that the claimed tablets comprised a further agent selected from:
(i) taurolidine or taurultam or a combination thereof,
(ii) a zinc amino acid chelate, and
(iii) tromethamole,
wherein the said agent was comprised in the outer layer of the fast release phase.

Hence, starting from D1, the technical problem to be solved by the present invention was the provision of improved means to treat H.pylori associated diseases. The solution to this problem was considered to be obvious in the light of D10 with regard to taurolidine and/or taurultam, of D4 with regard to the zinc amino acid chelate, and of D11 with regard to tromethamole, since all these agents were known in the treatment of H. pylori diseases.

D10 taught that taurolidine and taurultam eliminated the H. pylori resistance to antibiotic drug, and that their site of action was the stomach and the duodenum;

this necessitated a fast release, which made their incorporation in the outer layer obvious.

In view of D4, it was also obvious to incorporate the zinc amino acid chelate in the outer fast release layer, given the fact that D4 taught a direct effect on the gastric mucosal injury due to oxidative stress.

D11 taught that tromethamole was a pH-buffering agent, which inhibited the degradation of the PPI, and, in view of this mode of action, it was obvious to incorporate tromethamole in the fast outer release layer of the tablet.

The main request was not inventive and the auxiliary request equally failed for lack of inventive step for the same reason.

IV. The applicant (hereinafter the appellant) filed an appeal against the decision of the examining division. With the statement of grounds of appeal dated 20 July 2017, the appellant filed the following item of evidence:

D12: Comparative experiments - Annex I

V. A communication expressing the board's preliminary opinion was sent to the appellant. The Board stated *inter alia* that the main request and the auxiliary request did not appear to be inventive.

VI. With letter of 20 December 2019 the appellant submitted a new main request and auxiliary requests I-IV.

Claim 1 of the new main request read as follows, the difference with respect to the main request on which

the decision of the examining division was based being indicated in **bold** (addition):

"1. An oral pharmaceutical composition for treatment of Helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally at least one agent selected from the group consisting of taurolidine or taurultam or a combination thereof, a zinc amino acid chelate, tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the substance or substances selected from taurolidine or taurultam or a combination thereof, the zinc amino acid chelate, the tromethamole is/are comprised in the outer layer of fast release phase, **wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer**."

The subject-matter of claim 1 of the auxiliary requests read as follows, the difference with respect to the main request being indicated in **bold** (addition) or ~~stricken through~~ (deletion):

Auxiliary request I

"1. An oral pharmaceutical composition for treatment of helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,

- additionally at least one agent selected from the group consisting of taurolidine or taurultam or a combination thereof, a zinc amino acid chelate, tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the substance or substances selected from taurolidine or taurultam or a combination thereof, the zinc amino acid chelate, the tromethamole is/are comprised in the outer layer of fast release phase, **and the outer layer comprises the antibiotic or mixture of antibiotics**, wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer."

Auxiliary request II

"1. An oral pharmaceutical composition for treatment of helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally ~~at least one agent selected from the group consisting of~~ **i)** taurolidine or taurultam or a combination thereof, **ii)** a zinc amino acid chelate, **and iii)** tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the ~~substance or~~ substances ~~selected from~~ **i)** taurolidine or

taurultam or a combination thereof, **ii)** the zinc amino acid chelate, **and iii)** the tromethamole ~~is/~~are comprised in the outer layer of fast release phase, wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer."

Auxiliary request III

"1. An oral pharmaceutical composition for treatment of Helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally ~~at least one agent selected from the group consisting of~~ **i)** taurolidine or taurultam or a combination thereof, **ii)** a zinc amino acid chelate, **and iii)** tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the ~~substance or~~ substances ~~selected from~~ **i)** taurolidine or taurultam or a combination thereof, **ii)** the zinc amino acid chelate, **and iii)** the tromethamole ~~is/~~are comprised in the outer layer of fast release phase **and the outer layer comprises the antibiotic or mixture of antibiotics**, wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer."

Auxiliary request IV

"1. An oral pharmaceutical composition for treatment of Helicobacter pylori associated diseases comprising
- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally ~~at least one agent selected from the group consisting of~~ **i)** taurolidine or taurultam or a combination thereof, **ii)** a zinc amino acid chelate, **and iii)** tromethamole,
within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the ~~substance or~~ substances ~~selected from~~ **i)** taurolidine or taurultam or a combination thereof, **ii)** the zinc amino acid chelate, **and iii)** the tromethamole ~~is/~~are comprised in the outer layer of fast release phase, wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer, **the outer layer is formulated in a compressed form, and wherein the outer layer comprises the antibiotic or mixture of antibiotics.**"

VII. During the oral proceedings held on 3 February 2020 auxiliary request V was submitted.

The subject-matter of claim 1 of auxiliary request V read as follows:

"1. An oral pharmaceutical composition for treatment of Helicobacter pylori associated diseases being cancer comprising

- a proton pump inhibitor,
- an antibiotic or a combination of antibiotics,
- additionally i) taurolidine or taurultam or a combination thereof, ii) a zinc amino acid chelate, and iii) tromethamole,

within a fixed-dose combination for oral administration in the form of a biphasic release form which is formulated as biphasic tablets with an inner slow release layer and an outer fast release layer wherein the inner slow release layer is enteric coated and comprises the proton pump inhibitor and wherein the substance or substances i) taurolidine or taurultam or a combination thereof, ii) the zinc amino acid chelate, and iii) the tromethamole are comprised in the outer layer of fast release phase, wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer."

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

D1 was the closest prior art, and did not refer to a compressed tablet with enteric coating on the core comprising a pharmaceutically suitable plasticiser. D1 indicated that the oral composition may comprise antibacterial pentagastrin (PG), which was different from an antibiotic, a proton pump inhibitor (PPI) and possibly an antibiotic, in a great number of possible dosage forms, such as suspensions, capsules or tablets. It was clear from paragraph [0026] that the antibiotic was in a separated oral dosage form.

Accordingly, D1 did not suggest that the biphasic release form is a biphasic compressed tablet wherein the PPI was present in a compressed form in the core while the enteric coating comprised a pharmaceutically

suitable plasticiser; moreover, biphasic tablets were superior to monophasic tablets, as also shown in D12.

D1 did not suggest the presence of additional components like the agents recited in claim 1 as well as the antibiotic or combination of antibiotics.

Furthermore, in the compositions of D1 (par. [0068] to [0078]), the enteric coating layers were applied not to the compressed tablet as such, but to the granules containing the PPI.

A combination of D1 with D4, D10 or D11, in order to provide a biphasic tablet to increase the inhibition activity of the PPI and antibiotic, was not obvious.

Thus, the subject matter of the new main request was inventive over the prior art.

The same was true for auxiliary request I, which required that the outer layer comprised the antibiotic or the mixture of antibiotics.

The subject matter of auxiliary request II as well as of the further auxiliary requests specified the addition of taurolidine or taurultam or a combination thereof together with the zinc amino acid chelate and tromethamole. None of the prior art references identified that the combination of these three types of agents had a beneficial effect when combined with the PPI and the antibiotic.

The subject matter of auxiliary request III was inventive over the prior art, since the specific combination of agents was not suggested in any of the documents. Further, none of the documents described

the presence of the antibiotic or the mixture of antibiotics in the outer layer.

Auxiliary request IV further specified that the outer layer was formulated in a compressed form as it was the case for the inner layer. Moreover, in the compositions of this request only the PPI was present in the inner layer whereas the antibiotics and the other agents were present in the outer layer accordingly.

Auxiliary request V had to be admitted into the proceedings. Claim 1 was restricted to a specific medical indication, namely the treatment of cancer, for which an effect was explicitly shown in D12.

IX. Requests

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or one of auxiliary requests I to IV filed by letter of 20 December 2019 or auxiliary request V filed during the oral proceedings of 3 February 2020.

Reasons for the Decision

1. Main request - Inventive step

1.1 The invention relates to an oral composition for the treatment of Helicobacter pylori associated diseases.

1.2 In the examination proceedings, D1 was considered as the closest prior art.

Said document discloses the use of a proton pump inhibitor (PPI) in association with pentagastrin (PG) for the treatment and/or prevention of Helicobacter pylori associated diseases (see par. [0002]).

Pentagastrin is presented in D1 as an inhibitor of the growth enhancing effect of gastrin on H. pylori, and as possessing explicitly a local anti-bacterial effect in the stomach and a synergistic effect in eradicating H. pylori (see par. [0010] and [0014]). In this sense, as also pointed out by the examining division in its decision, pentagastrin can be considered as an antibiotic, since the broadest definition of an antibiotic is a medicine that inhibits the growth of microorganisms, or destroy them. This, all the more since the list of suitable "antibiotics" disclosed in the application is very broad, is not limited to classis antibiotics such as penicillins derivatives, but comprises also compounds such as tinidazole, nitrofurantoin, furazolidone, chlorhexidine, etc... (see lists of antibiotics on pages 7 and 8 of the application and claim 2 as originally filed for tinidazole). The term "antibiotic" must therefore be understood and interpretated in a broad sense and pentagastrin can be regarded as representing an antibiotic.

D1 discloses specifically in paragraphs [0025] and [0026] the preparation of an oral composition in the form of a tablet or a capsule comprising a PPI, PG and also an unspecified antibiotic; the PPI may be enteric coated. A preferred dosage form is a tablet comprising enteric coated omeprazole as PPI in the core, and PG in an immediate release-type coating layer, i.e. a biphasic tablet with the PPI in enteric coated form in the inner layer, and an outer layer with PG.

D1 does not disclose explicitly the additional presence of (i) taurolidine or taurultam or a combination thereof, (ii) a zinc amino acid chelate, and (iii) tromethamole. However, it envisages the addition of a pH-buffering agent, such as tromethamole in the compositions (see D1, par. [0067]).

1.3 According to the appellant, the problem is the provision of biphasic tablets which are superior to monophasic tablets because they increase the inhibition activity of the PPI and of the antibiotic.

1.4 The solution is a biphasic tablet comprising *inter alia* at least one agent selected from the group consisting of taurolidine or taurultam or a combination thereof, a zinc amino acid chelate, tromethamole,
wherein the biphasic release form is a biphasic compressed tablet with an enteric coating on the core comprising a pharmaceutically suitable plasticizer.

1.5 The appellant provided experimental evidence with its statement of grounds of appeal to demonstrate a superior effect linked with biphasic oral compositions.

1.5.1 Said tests (document D12) provide indeed a comparison between monophasic tablets and biphasic tablets. The monophasic tablets comprise a PPI, an antibiotic and a combination of three or four of taurolidine or taurultam, a zinc amino acid chelate, and tromethamole. The biphasic tablet comprises the PPI and/or the antibiotic(s) in the inner slow layer, and three or four of taurolidine, taurultam, a zinc amino acid chelate, and tromethamole with or without the antibiotic(s) in the outer fast release layer. The biphasic tablet shows an improved effect as to gastric

cancer cell inhibition and in gastric cancer cell viability, versus the monophasic tablets.

1.5.2 The tablets disclosed in D1 are however also biphasic tablets wherein the PPI is enteric coated, and not monophasic tablets. Thus, the comparative tablets used in the experiments of D12 do not reflect the teaching of D1. Therefore, the tests of D12 do not allow any comparison to be made with the compositions of the closest prior art.

Additionally, all tablets tested in D12 comprise at least three of taurolidine, taurultam, a zinc amino acid chelate, and tromethamole, while claim 1 of the main request encompasses also tablets comprising only one or two of these ingredients. Hence, the results of these tests cannot be extrapolated to the whole scope of claim 1.

1.5.3 For all these reasons, the Board considers that there is no effect demonstrated over the closest prior art, and the technical problem must be reformulated as the provision of an alternative biphasic tablet.

1.6 The question remaining is whether the skilled person, starting from the teaching of D1, would arrive at the subject-matter of claim 1 of the main request in an obvious manner in order to solve the problem posed.

In the Board's view, it belongs to the normal activity of the skilled person to accomplish routine modifications.

Hence, coating the inner layer instead of coating the PPI in the inner layer constitutes an obvious routine

modification for the skilled person, which has no incidence on the release of the PPI.

This also applies to the compressed form of the tablet and the presence of a plasticizer in the enteric coating, which are immediately obvious routine options in the manufacture of tablets. Indeed, tablets are usually in compressed form, and an enteric coating usually comprises a plasticizer.

Finally, D1 suggests the addition of tromethamole as pH buffering agent, which constitutes therefore also an obvious modification. Moreover, as discussed by the examining division in its decision (see point IV above), taurolidine or taurultam, zinc amino acid chelates, and tromethamole were known in the treatment of H. pylori as shown by D10, D4 and D11. The skilled person would consider obvious their incorporation in the biphasic compositions of D1. Their mode of action by a direct local activity, as disclosed in D10, D4 and D11 would furthermore incite the skilled person to incorporate them in a form immediately available in the stomach, thus in a fast release outer layer of a tablet as disclosed in D1 (see D10, claims and column 4, lines 22-25; see D4, Abstract; see D11, [0043] and [0045]).

Consequently, the claimed solution is obvious and claim 1 of the main request lacks inventive step (Article 56 EPC).

2. Auxiliary request I - Inventive step

Claim 1 of this request is further restricted by the feature "and the outer layer comprises the antibiotic or mixture of antibiotics".

This restriction does not involve a further difference over the disclosure of D1, since PG was in the outer layer of the tablet disclosed therein. It has therefore no impact on the assessment of inventive step over D1.

Consequently, auxiliary request 1 does not meet the requirements of inventive step (Article 56 EPC).

3. Auxiliary request II -Inventive step

In comparison to claim 1 of the main request, claim 1 of auxiliary request II has been restricted by the requirement that all the agents are included in the composition (see feature: "additionally i) taurolidine or taurultam or a combination thereof, ii) a zinc amino acid chelate, **and** iii) tromethamole") and by the indication that these agents "are comprised in the outer layer of fast release phase".

As mentioned by the examining division in its decision and argued above for the main request, taurolidine or taurultam, zinc amino acid chelates, and tromethamole were known in the treatment of H. pylori as shown by respectively D10, D4 and D11. Neither the application, nor the experiments D12 demonstrate that the association of all three classes of agent would provide a synergistic, unexpected or even improved effect in combination with a PPI and an antibiotic as claimed.

Since there is no effect demonstrated over the teaching of the prior art, the problem remains the provision of an alternative biphasic tablet.

As for the main request, coating the inner layer, providing the tablets in compressed form, and using a

plasticizer in the enteric coating are obvious routine options in the manufacture of tablets.

The skilled person would also consider the incorporation of i) taurolidine or taurultam or a combination thereof, ii) a zinc amino acid chelate, and iii) tromethamole in a biphasic composition as disclosed in D1 as an obvious measure, since these agents are known for acting in the treatment of H. pylori associated diseases, alone or in combination with a PPI. As already argued for the main request, the local mode of action of the agents i), ii) and iii), which is disclosed in D10, D4 and D11, would furthermore incite the skilled person to incorporate them in a form immediately available in the stomach, thus in a fast release outer layer of a tablet as disclosed in D1.

The subject-matter of claim 1 of auxiliary request II is therefore obvious, and auxiliary request II does not meet the requirements of Article 56 EPC.

4. Auxiliary request III -Inventive step

Claim 1 of auxiliary request III differs from claim 1 of the main request in that it incorporates the limiting features included in auxiliary requests I and II.

As argued above in respect of the previous auxiliary requests, each of these restrictions cannot render the claimed subject-matter inventive, and a combination of both restrictions cannot change the conclusion on inventive step in the absence of any effect demonstrated over the teaching of the prior art.

Consequently, auxiliary request III lacks inventive step (Article 56 EPC).

5. Auxiliary request IV -Inventive step

In comparison to claim 1 of auxiliary request III, claim 1 of auxiliary request IV has been further restricted by the feature "the outer layer is formulated in a compressed form".

As for the previous requests, there is no effect demonstrated over the teaching of the prior art, the problem remains the provision of an alternative biphasic tablet.

This amendment has no incidence on the assessment of obviousness over D1, since the compressed form of the outer layer is an immediately obvious routine option in the manufacture of tablets.

Consequently, the subject-matter of claim 1 of auxiliary request IV is obvious and auxiliary request IV does not meet the requirements of Article 56 EPC.

6. Auxiliary request V - Admission into the proceedings

This request has been filed at a very late stage of the proceedings, namely during oral proceedings, and after the Board announced that none of the requests on file met the requirements of Article 56 EPC.

Claim 1 of auxiliary request V specifies the medical indication, namely cancer. This specific medical indication does not originate from a dependent claim, but from the description.

Such amendment would imply the opening of a new discussion on inventive step and constitutes a fresh case at a very late stage of the appeal proceedings. Even if document D1 mentions the treatment of "gastric carcinoma" in its dependent claim 6, there is indeed no certainty that D1 will remain the closest prior art.

In the Board's view, auxiliary request V relates to a new subject which has never been treated by the examining division, and which cannot be examined for the first time in the appeal stage because this would imply a substantial change of the subject of discussion that would necessitate an adjournment of the oral proceedings, or even a remittal to the examining division, situations which would both be contrary to the principle of procedural economy.

Consequently, auxiliary request V is not admitted into the proceedings (Article 13(3) RPBA 2007).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated