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Datasheet for the decision of 6 November 2014

Case Number: T 0100/11 - 3.3.07

Application Number: 04705487.9

Publication Number: 1596838

IPC: A61K9/24, A61K9/26, A61K9/36, A61K9/62, A61K9/58

Language of the proceedings: EN

Title of invention:
ONCE A DAY ORALLY ADMINISTERED PHARMACEUTICAL COMPOSITIONS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT

Applicant:
Torrent Pharmaceuticals Ltd

Headword:

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1), 13(3)

Keyword:
Inventive step - main request (no)
Late-filed request - admitted (no)

Decisions cited:

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Catchword:

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Case Number: T 0100/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 6 November 2014

Appellant: (Applicant)	Torrent Pharmaceuticals Ltd Torrent House, Near Dinesh Hall, Off Ashram Road Ahmedabad 380 009, Gujarat State (IN)
Representative:	Matthews, Derek Peter Dehns St Bride's House 10 Salisbury Square London EC4Y 8JD (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 July 2010 refusing European patent application No. 04705487.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	D. T. Keeling

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division announced at the oral proceedings on 22 June 2010 to refuse European patent application No 04 705 487.9.

II. The documents cited during the examination proceedings included the following:

D1: WO 97/25065
D2: WO 00/51583
D5: Acta Pharm. 49, 1999, 267-273

III. The decision was based on a main request and two auxiliary requests.

Claim 1 of the main request read as follows:

"1. A pharmaceutical composition for once a day oral administration, comprising

A) proton pump inhibitor in delayed release form,

B) prokinetic agent in sustained release dosage form, wherein the said dosage form of prokinetic agent is selected from

i. single layer or bilayer matrix tablet comprising prokinetic agent and sustained release matrix-forming hydrophilic polymer selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, poly(ethylene oxide), poly(vinyl alcohol), xanthan gum, carbomer, carrageenan, carboxymethyl cellulose, sodium alginate or mixtures thereof and

ii. multiparticulate system comprising core coated with rate controlling polymer selected from ammonio methacrylate co-polymers,

wherein the said sustained release prokinetic agent exhibits the following dissolution profile

5 to 70% pro-kinetic agent is released in one hour, 15 to 80 % prokinetic agent is released in four hours, 25 to 90 % prokinetic agent is released in eight hours, 35 to 100 % prokinetic agent is released in twelve hours."

Claim 1 of auxiliary request 1 and claim 1 of auxiliary request 2 were based on claim 1 of the main request and differed therefrom respectively in the indication of the amount of the hydrophilic polymer and in the limitation of the latter to hydroxypropylmethyl cellulose

IV. The decision of the examining division can be summarised as follows:

a) Document D1 was the closest prior art for the assessment of inventive step of the main request. The claimed subject-matter differed from the compositions disclosed in this document, such as the tablet of example 2, in the specific dissolution profile of the prokinetic agent. The applicant did not provide convincing arguments that all the hydrophilic polymers listed in claim 1 would have provided a sustained release of the prokinetic agent. The technical problem was therefore to be seen in the provision of an alternative formulation comprising a proton pump inhibitor in delayed release form and a prokinetic agent. The provision of a merely alternative formulation could not justify the presence of an

inventive step, because the choice of the hydrophilic polymers was only the result of an arbitrary selection.

b) The limitations introduced in the first and second auxiliary requests were also to be regarded as arbitrary choices which did not result in any particular effect. Thus, also the subject-matter of the auxiliary requests was considered obvious.

V. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal sent on 13 December 2000, the appellant sent four sets of claims consisting of a main request and three auxiliary requests. The claims of the main request were identical to the claims of the main request refused by the examining division.

VI. On 1 August 2014 the Board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Board of Appeal (RPBA; OJ EPO 2007). In this communication, the Board observed with regard to the requirements of Article 123(2) EPC, that the feature "bilayer matrix tablet" was disclosed in the application as originally filed, in relation to tablets comprising a sustained release layer and an immediate release layer. The omission from claim 1 of all the requests of any reference to the presence of an immediate release layer appeared to represent a generalisation of the disclosure provided by the original application. The communication contained also some considerations concerning the assessment of inventive step.

VII. With letter of 6 October 2014 the appellant submitted a new set of claim as main request and withdrew all the requests submitted on 13 December 2000.

Claim 1 of the new main request differed from claim 1 of the main request refused by the examining division (see point III above) in that the component B) was defined in the following manner:

"B) prokinetic agent in sustained release dosage form, wherein the said dosage form of prokinetic agent is single layer or bilayer matrix tablet comprising prokinetic agent and sustained release matrix-forming hydrophilic polymer selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, poly(ethylene oxide), poly(vinyl alcohol), xanthan gum, carbomer, carrageenan, carboxymethyl cellulose, sodium alginate or mixtures thereof, wherein said bilayer matrix tablet further comprises an immediate release layer containing prokinetic agent,..."

The dissolution profile of the prokinetic agent remained unchanged.

VIII. Oral proceedings were held on 6 November 2014. During the oral proceedings the appellant submitted a new set of claims as an auxiliary request.

Claim 1 of this request differed from claim 1 of the main request filed on 6 October 2014 in that the dosage form of the prokinetic agent was limited to the bilayer matrix tablet (i.e. the feature "single layer" was deleted).

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

a) Main request - Inventive step

The closest prior art was document D1 which related to compositions comprising a proton pump inhibitor and a prokinetic agent. This document did not disclose a once-daily dosage form. The reference on page 7 to the possibility of formulating the prokinetic part in the form of sustained release was purely speculative. In fact D1 did not exemplify any composition containing a prokinetic agent in such dosage form. In particular, contrary to the position taken by the examining division, in the composition of example 2 the prokinetic agent was not in a sustained release dosage form. Document D1 also did not mention any process of preparation of such formulation. The technical problem was to be seen in the provision of new and improved pharmaceutical compositions of a proton pump inhibitor and a prokinetic agent which exhibited suitable dissolution profile to render them suitable for once a day oral administration. A skilled person would have disregarded the speculative disclosure of page 7 of document D1 with respect to preparation of a sustained release formulation of prokinetic agent. It was to be appreciated that development of a fixed dose combination with required release profile was a challenge to the formulator particularly in the present case in which the two active ingredients had different pharmacokinetic profiles. The disclosure of document D1 was too generic to provide any relevant information in that respect. Even taking into account document D5 there was no lack of inventive step, as this disclosed controlled release formulations of carbamazepine only and did not teach to prepare any dosage forms having combinations of two different active ingredients.

b) Auxiliary request - Admissibility

The amendments introduced in claim 1 of the auxiliary request had the effect of limiting the subject-matter of the main request to compositions in which the prokinetic agent was in a bilayer matrix tablet. These compositions were illustrated by various examples. The presence of an immediate release layer in the bilayer matrix tablet resulted in a better release profile. None of the cited documents suggested compositions in which the prokinetic agent was formulated in a bilayer matrix tablet comprising an immediate release layer. Hence, the subject-matter of auxiliary request fulfilled the requirements of Article 56 EPC.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request appended to its letter of 6 October 2014 or, in the alternative, on the basis of the claims of the auxiliary request submitted during the oral proceedings

Reasons for the Decision

Main request

1. *Admissibility*

This request was filed on 6 October 2014, i.e. when oral proceedings had already been arranged. The admissibility of this request is therefore at the Board discretion (Articles 13(1) and 13(3) of the Rules of Procedure of the Board of Appeal (RPBA), Supplementary publication to OJ EPO 1/2014, 44). The amendments introduced in claim 1 of this request address the objection under Article 123(2) EPC raised by the Board in its communication of 1 August 2014 in respect to the requests filed with the statement of the grounds of appeal (see points VI and

VII above). The Board decides therefore to admit this request into the proceedings.

2. *Inventive Step*

The application is directed to pharmaceutical compositions for once-a-day administration comprising a a proton pump inhibitor in delayed release form and a prokinetic agent in sustained release form.

2.1 *Closest prior art*

2.1.1 The Board agrees with the examining division and with the appellant that document D1 represents the closest prior art. This document relates to oral pharmaceutical dosage forms comprising the same classes of active ingredients of the compositions of the application in suit, namely a proton pump inhibitor and a prokinetic agent.

2.1.2 The proton pump inhibitor is constituted by individual units covered by an enteric coating layer (page 5, lines 18-20). As stated in the appealed decision (see 1.1), the effect of the enteric coating is to delay the release of the proton pump inhibitor. This was not disputed by the appellant. Accordingly, the compositions disclosed in D1 can be considered to comprise a proton pump inhibitor in delayed release form.

2.1.3 As to the prokinetic agent, it is explained on page 7 of D1 that this can be formulated in the form of instant release, sustained release or extended release. There is however no explicit indication as to which one of these formulations has been used in the compositions of examples 1 to 14. The Board accepts the position expressed by the appellant that none of the examples of

D1 relates to compositions containing the prokinetic agent in sustained release form.

2.1.4 It is furthermore explained in document D1 that the dosage forms disclosed therein are administered several times a day, preferably once or twice daily (page 22, lines 26,27). There is however no indication as to the frequency of administration of the specific compositions prepared in examples 1 to 14. The Board agrees with the applicant that none of these composition appears suitable for a single daily administration.

2.1.5 In view of the observations made in points 2.1.3 and 2.1.4 above, the Board considers that D1 fails to provide an unambiguous disclosure of compositions containing the prokinetic agent in sustained release dosage form which are suitable for once-a-day administration.

2.2 *Technical problem*

2.2.1 The technical problem underlying the invention in the light of document D1 can therefore be seen in the provision of an alternative composition comprising a proton pump inhibitor in delayed release form and a prokinetic agent.

2.2.2 As a solution to this problem the application proposes a composition which is suitable for once-a-day administration and is characterised in that the prokinetic agent is formulated according to the sustained release dosage forms defined in claim 1 and exhibits a specific dissolution profile as defined in the claim.

2.2.3 The application discloses various examples of pharmaceutical compositions according to claim 1. The data relating to the dissolution profile reported in these examples show that the prokinetic agent is released in a sustained release manner while the proton pump inhibitor is almost entirely released in the intestinal fluid. Furthermore, from the bioequivalence data provided in examples 17 and 18 it is apparent that the plasma concentration of the active ingredients is maintained in such a way that once-a-day administration is possible. The Board considers therefore that the technical problem defined in point 2.2.1 above has been effectively solved by the provision of the composition of claim 1.

2.3 *Obviousness*

2.3.1 As mentioned above, in the first sentence of page 7 of D1, it is explained that the prokinetic agent can be formulated in three alternative dosage forms, one of which is the sustained release form. Hence, the closest prior art provides a clear hint to formulate the prokinetic agent as in the compositions of the present invention.

In the Board's opinion, the absence in D1 of examples relating to compositions in which the prokinetic agent is actually formulated in a sustained release dosage form, would not lead the skilled person to rate the suggestion of D1 for this type of formulations as a pure speculation, as suggested by the appellant. In this respect it is observed that there are no prior art documents suggesting that some exceptional technical difficulties may arise in formulating a prokinetic agent in a sustained release form. The Board acknowledges that the presence in the pharmaceutical composition of an

additional active ingredient may render the task of the formulator more complicated. However, no evidence was submitted by the appellant to support the existence of some insurmountable technical difficulties arising from the combination of a prokinetic agent and a proton pump inhibitor. Hence, the Board sees no reasons for assuming that the clear indication of D1 as to the possibility of formulating the prokinetic agent in a sustained release form would be considered by the skilled person as unfeasible because not supported by examples.

2.3.2 In the light of the above, the Board concludes that the skilled person, faced with the problem defined in point 2.2.1 above, would regard the suggestion of document D1 to formulate the prokinetic agent in a sustained release dosage form as a possible solution. It must therefore be assessed whether he would choose one of the specific dosage forms mentioned in claim 1.

In this respect the Board considers that the skilled artisan in the field of pharmaceutical formulations has knowledge of various technologies for obtaining a sustained release effect of an active ingredient. These include also the use of the polymer-based matrix systems specified in claim 1. For instance, the authors of document D5, which was published in 1999, describe the use of hydroxypropyl methylcelluloses (HPMC) for the preparation of slow-release matrix-tablets containing carbamazepine as active ingredient. HPMC is one of the matrix-forming sustained release polymers mentioned in claim 1 of the application. The appellant correctly observed that D5 relates to formulations containing as active ingredient carbamazepine, i.e. a substance which does not belong to the class of the prokinetic agents. However, it is affirmed in the same document (page 268, paragraph following equation (4)) that HPMCs are used in

many retard dosage forms and that HPMC matrices provide various advantages with respect to dissolution rate. In the same paragraph the authors of D5 provide some references to previous prior art articles. In the Board's opinion these passages suggest that well before the priority date of the present application, HPCM was a known agent for the preparation of sustained release matrix tablets and that its application was not limited to any specific active ingredient. This finds a confirmation for instance in document D2 in which HPMC is mentioned as a polymer useful for the preparation of controlled release compositions (page 19, line 13). In this case the pharmaceutical compositions do not contain carbamazepine as active ingredient.

In the light to the above, the Board considers that providing a sustained release dosage form consisting of a matrix tablet made of HPMC does not involve any inventive activity.

2.3.3 As to the characteristic of the pharmaceutical compositions of being suitable for once-a-day administration, the Board considers that this effect is a direct consequence of the sustained release profile of the prokinetic agent. It is evident that a dosage form which allows the release of the active ingredient over an extended period of time, such as a sustained release formulation, has the advantage of reducing the number of administrations. Since formulating the prokinetic agent in a sustained release form is taught by D1, it follows that by implementing this teaching it is possible to reduce the frequency of administration. Indeed it is no coincidence in the Board's opinion that the once-a-day administration is contemplated also in D1 (page 22, lines 25-27).

2.3.4 Claim 1 defines also the release profile of the prokinetic agent in terms of percentage of drug released as a function of the time. The description does not contain any data showing the existence of any particular effect associated with this release profile. Nor has the appellant submitted any argument in this respect. In the Board's opinion, the features describing the release profile of the prokinetic agent merely confirm that this substance is formulated in a sustained release form and therefore they do not provide any inventive contribution to the subject-matter of the claim.

2.4 It follows from the above that the subject-matter of claim 1 does not involve an inventive step.

Auxiliary request

3. *Admissibility*

3.1 The auxiliary request was filed during the oral proceedings held on 6 November 2014. Claim 1 of this request differs from claim 1 of the main request in the dosage form of the prokinetic agent, which is limited to the bilayer matrix tablets.

Questioned by the Board as to the relevance of the amendment introduced in claim 1 for the assessment of inventive step, the appellant argued that the presence of an immediate layer in the bilayer matrix tablets determined an improvement of the pharmacokinetic profile of the prokinetic agent, which was not suggested in the prior art documents.

3.2 The Board notes that in none of the requests upon which the appealed decision was based did claim 1 contain the feature relating to the presence of an immediate release

layer. This feature was likewise absent from claim 1 of the four requests submitted to the Board with the statement setting out the grounds of appeal. It was only with the set of claim filed on 6 October 2010 that claim 1 was amended to recite an additional immediate release layer. However, in the letter accompanying this set of claims, the appellant explained that the feature concerning the immediate release layer was introduced in claim 1 in response to the Article 123(2) issues noted by the Board in the communication of 1 August 2014 (see point VI above). Indeed in the same letter no reference was made to this feature in the context of the discussion concerning Article 56 EPC.

3.3 By relying on the technical effects determined by the introduction of the immediate release layer, the appellant is therefore developing a new line of defence which was never invoked until the oral proceedings and upon which also the examining division did not take position in its decision. This line of defence could not be expected by the Board in view of the fact that the new feature was apparently introduced only in reply to an objection under Article 123(2) EPC.

To examine the relevance of the new request, the Board would be obliged to assess the effects alleged by the appellant and analyse the prior art documents in the light of these new effects. This would raise new issues which the Board cannot reasonably be expected to deal with during the oral proceedings.

3.4 In view of this, the Board considers it appropriate to exercise its discretion under Articles 13 (1) and (3) RPBA by not admitting the auxiliary request into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated