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Datasheet for the decision of 24 May 2007

Case Number: T 0702/04 - 3.3.02

Application Number: 00203970.9

Publication Number: 1093812

IPC: A61K 31/42

Language of the proceedings: EN

Title of invention:
Amoxycillin and clavulanate containing pharmaceutical formulation

Applicant:
SMITHKLINE BEECHAM PLC

Opponent:
-

Headword:
Amoxycillin/clavulanate formulation/SMITHKLINE BEECHAM

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request: inventive step (no), increase in amoxycillin: clavulanate weight ratio obvious in the light of closest prior art"

Decisions cited:
-

Catchword:
-

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Case Number: T 0702/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 24 May 2007

Appellant: SMITHKLINE BEECHAM PLC
New Horizons Court
Brentford
Middlesex TW8 9EP (GB)

Representative: Connell, Anthony Christopher
GlaxoSmithKline
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 16 October 2003 refusing European application No. 00203970.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
P. Mühlens

Summary of Facts and Submissions

I. European patent application No. 00 203 970.9 published as EP 1 093 812 is a divisional application of the parent application No. 96 930 817.0 published as EP 0 862 431.

The appeal lies from a decision of the examining division refusing the patent application under Article 97(1) EPC.

The decision was based on a main request, a first auxiliary request, and a second auxiliary request all filed with the letter of 18 June 2003.

Claim 1 of the main request read as follows:

"1. A pharmaceutical formulation comprising amoxycillin and clavulanate in a weight ratio of 16:1."

II. The following document was cited inter alia during the proceedings:

(14) WO 94/16696

III. The examining division considered that the subject-matter of the main request lacked an inventive step (Article 56 EPC).

The examining division argued that the whole development illustrated by a number of prior art documents clearly showed a tendency towards increased amounts of amoxycillin relative to clavulanate, and it was therefore considered to be within the normal

routine of a skilled person to adapt the existing formulations in this direction.

The examining division defined the problem to be solved as lying in the provision of a further pharmaceutical formulation with improved properties in the treatment of bacterial infections.

In the examining division's opinion, the claimed solution had not been convincingly proven to imply an unexpected effect over the known 12:1 formulation.

Concerning the first and second auxiliary requests, the examining division considered that the subject-matter claimed did not fulfil the requirements of Articles 76(1) and 123(2) EPC, and lacked an inventive step (Article 56 EPC).

IV. The appellant (applicant) lodged an appeal against said decision and filed an auxiliary request to replace the auxiliary requests on file.

V. Following a communication by the board, the appellant submitted an amended request (claims 1 to 6) with the letter of 30 January 2007, which differed from the previous main request in that claims 4 to 6 and 10 to 13 had been deleted, and the remaining claims and dependencies renumbered accordingly. The appellant stated that the newly filed set of claims was "to replace the claims presently on file".

VI. In the communication accompanying the summons to oral proceedings, the board pointed to the fact that the request filed with the letter of 30 January 2007 was

considered to be the main and sole request. This was not disputed by the appellant in its subsequent letter of 2 May 2007.

VII. With said letter of 2 May 2007, the appellant announced that it would not be attending oral proceedings.

VIII. Oral proceedings were held before the board on 24 May 2007 in the absence of the appellant.

IX. Insofar as they are relevant to the present decision, the appellant's arguments submitted in writing in support of an inventive step for the subject-matter claimed may be summarised as follows:

The appellant argued that the formulations of the invention were intended for the empirical treatment of bacterial infections, in particular respiratory tract infections, where there is a concern that the causative organism may be DRSP (drug-resistant Streptococcus pneumoniae).

The appellant considered document (14) to represent the closest state of the art, because the problem of treating resistant organisms, including resistant strains of *S. Pneumoniae*, was specifically addressed therein.

Having regard to document (14), the appellant defined the problem to be solved as lying in the provision of a new formulation to support a new dosage regimen for treating PRSP (penicillin-resistant *S. Pneumoniae*).

The appellant considered that, whilst the broadest ratio of antibacterial agent to clavulanate disclosed in document (14) was from 1:1 to 30:1, the preferred range of amoxycillin to clavulanate was 1:1 to 12:1 and the exemplified ratio corresponded to 4:1. The appellant argued that the skilled person was therefore directed towards the lower end of the ratio range, away from the present ratio of 16:1. In addition, the appellant was of the opinion that the teaching from document (14) was to use more clavulanate rather than less, that is, to move to a lower ratio than 4:1. Even if the skilled person was to move to a higher ratio, he would go no further than 12:1, the upper limit specified for amoxycillin to clavulanate.

Furthermore, the appellant argued that the formulation as claimed provided an improved pharmaceutical formulation for treating bacterial infections. In support thereof, the appellant referred to the approval in the USA of the product "Augmentin XR" for use in a dosage regimen of 2000/125 mg of amoxycillin and clavulanate (ratio 16:1) administered twice daily (bid), for treating respiratory tract infections associated with more resistant strains of *S. pneumoniae*, in adults. The appellant compared this regimen to the existing regimen of 875/125 mg bid (ratio 7:1).

In addition, the appellant referred to the data in example 3 of the application in suit as demonstrating that a dosage in the ratio of 14:1 was significantly more effective than a dosage in the ratio of 7:1 against three different resistant strains of *S. pneumoniae*.

X. The appellant (applicant) requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the main (sole) request filed with the letter of 30 January 2007.

Reasons for the Decision

1. The appeal is admissible.

2. Main and sole request

2.1 The present main request corresponds to claims 1-3 and 7-9 of the main request on which the first instance decision was based. No objections have been raised by the examining division under Articles 76(1) EPC and 123(2) EPC in the decision under appeal, and the board sees no reason to differ.

2.2 Since none of the cited prior art documents disclose a pharmaceutical formulation comprising amoxycillin and clavulanate in a **weight ratio of 16:1**, the novelty of the subject-matter of the present claims can be acknowledged (Articles 52(1) and 54 EPC).

2.3 Inventive step

Document (14) represents the closest prior art. This has not been disputed by the appellant.

This document relates to the provision of formulations for the treatment of bacterial infections caused by β-lactamase negative penicillin resistant pathogens such as *S. pneumoniae* (in addition to some β-lactamase

positive strains). In particular, document (14) discloses the treatment of respiratory tract infections (see page 4, lines 2-9).

The pharmaceutical compositions disclosed in document (14) comprise clavulanic acid in the form of clavulanate preferably in combination with an antibacterial agent such as a β-lactam antibiotic (page 2, lines 17-24). Amoxycillin is a preferred β-lactam antibiotic (cf. page 4, lines 13-16).

The weight ratio of clavulanate to antibacterial agent is disclosed as varying within a wide range, for example, from 1:1 to 1:30, more particularly, from 1:1 to 1:12 (page 7, lines 12-17).

A preferred combination is clavulanate with amoxycillin in a ratio range from 1:1 to 1:12 (page 7, lines 27-29).

Having regard to this prior art, the problem to be solved lies in the provision of a further pharmaceutical formulation comprising amoxycillin and clavulanate.

The solution as defined in claim 1 relates to a formulation characterised by the fact that the weight ratio of amoxycillin to clavulanate is 16:1.

On the basis of the disclosure of the claimed invention in the patent application, and in the absence of any evidence to the contrary, the board is satisfied that the problem stated above has indeed been solved.

It remains to be investigated whether the proposed solution is obvious to the skilled person in the light of the prior art.

As outlined above, document (14) discloses pharmaceutical formulations comprising amoxycillin and clavulanate as well as their use in combating bacterial infections caused by DRSP. In addition, document (14) discloses the combination of amoxycillin and clavulanate in a ratio of 12:1 in an individualised form.

In the general section dealing with the possible ratios of clavulanate to antibacterial agent, document (14) teaches that the formulations may, for example, contain up to 30 times more by weight of the antibacterial agent relative to clavulanate.

Accordingly, the skilled person faced with the problem defined above is led by the teaching of document (14) to modify the proportions of antibacterial agent relative to clavulanate. Hence, the increase of the ratio of amoxycillin to clavulanate from 12:1 to 16:1 must be viewed as being an obvious modification within the teaching of document (14).

Consequently, the subject-matter of claim 1 of the main request lacks an inventive step (Article 56 EPC).

In view of the above conclusion it is not necessary to comment on the remaining independent claims.

2.4 The appellant's arguments in favour of inventive step do not hold for the following reasons:

2.4.1 With respect to the appellant's argument that the teaching of document (14) would dissuade the skilled person from going to amoxycillin to clavulanate ratios of greater than 12:1, it has to be noted that the teaching of document (14) is not confined to its preferred embodiments.

As outlined above, ratios of antibacterial agent to clavulanate are generally disclosed in document (14) to be from 30:1 to 1:1. Thus, the amount of clavulanate is taught in document (14) to be at most equal to **or much lower than** the amount of antibacterial agent.

Consequently, it cannot be accepted that, starting from the ratio of 4:1 specifically exemplified, the skilled person is taught by document (14) to use more clavulanate rather than less.

Similarly, the fact that the preferred range disclosed in document (14) for the ratio of amoxycillin to clavulanate has an upper limit of 12:1 cannot be regarded as representing a technical prejudice that would dissuade the skilled person from applying the more general teaching of document (14).

2.4.2 The appellant's arguments in favour of an inventive step on the basis of an improvement of the pharmaceutical formulation as claimed over known products cannot be accepted for the following reasons:

According to the consistent case law of the boards of appeal, if comparative tests are chosen to demonstrate an inventive step with an improved effect, the

comparison must be with the closest state of the art and be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention.

The only distinguishing feature of the subject-matter as claimed in present claim 1 is the weight ratio of amoxycillin to clavulanate of 16:1.

In the comparisons referred to by the appellant, the ratio of amoxycillin to clavulanate is increased by increasing the daily dosage of amoxycillin and keeping the daily dosage of clavulanate constant (see grounds of appeal, item 6: dosage regimen of amoxycillin/clavulanate 2000/**125** mg bid (ratio 16:1) versus 875/**125** mg bid (ratio 7:1); and example 3 of the application in suit: 45/**3.2** mg/kg bid (ratio 14:1) versus 22.5/**3.2** mg/kg bid (ratio 7:1)).

Based on this evidence alone, it cannot be concluded that the characterising feature of the invention, i.e. the ratio of amoxycillin to clavulanate of 16:1, is at the origin of any improvement, independently of the absolute daily amounts of the active ingredients administered. Thus, for example, no conclusion can be reached as to whether any improvement would be maintained were the ratio of amoxycillin to clavulanate to be increased by keeping the daily dosage of amoxycillin constant and decreasing the daily dosage of clavulanate.

Moreover, in the evidence advanced by the appellant as outlined above, comparison was not made between the pharmaceutical formulation as claimed

(amoxycillin:clavulanate 16:1) and the closest state of the art, which is the combination of amoxycillin and clavulanate in a ratio of 12:1 disclosed in individualised form in document (14). No conclusion can therefore be drawn as to the relative merits of these two formulations.

Consequently, it cannot be concluded that the claimed subject-matter plausibly solves the purported problem of providing an improved pharmaceutical formulation.

2.5 Thus, the main and sole request is rejected for lack of inventive step (Articles 52(1) and 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald