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**Datasheet for the decision
of 31 July 2007**

Case Number: T 0214/04 - 3.3.02

Application Number: 01201824.8

Publication Number: 1147771

IPC: A61K 31/42

Language of the proceedings: EN

Title of invention:

Pharmaceutical formulation containing amoxicillin and clavulanate

Patentee:

SMITHKLINE BEECHAM PLC

Opponent:

-

Headword:

Amoxicillin/clavulanate formulation/SMITHKLINE BEECHAM

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main request: inventive step (no), obvious combination of prior art teachings"

Decisions cited:

-

Catchword:

-

Case Number: T 0214/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 31 July 2007

Appellant:

SMITHKLINE BEECHAM PLC
New Horizons Court
Brentford,
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Representative:

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted 16 June 2003
refusing European application No. 01201824.8
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. 01 201 824.8 published as EP 1 147 771 is a divisional application of the parent application No. 96 930 817.0, which was filed as international application WO 97/09042.

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

The decision was based on the main request filed with the fax of 28 January 2003, and on the first and second auxiliary requests filed with the letter of 10 January 2003.

Claim 1 of the main request read as follows:

"1. A pharmaceutical formulation comprising amoxicillin and clavulanate which is in the form of a powder or granular product adapted for reconstitution into a suspension or solution and is further adapted to provide a unit dosage of from 75 to 115 mg/kg/day of amoxicillin and from 5 to 7.5 mg/kg/day of clavulanate for a paediatric patient, which unit dosage is administered every 12h, such that the ratio of amoxicillin and clavulanate is 14:1."

- II. The following documents were cited inter alia during the proceedings:

- (1) S. Baron, P. Bégué, Ann. Pédiatr., 1991, 38(8), 549-555
- (8) WO 91/15197

(23) WO 94/16696

(26) J. Astruc, *Ann. Pédiatr.*, 1992, 39(2), 142-148

(28) R. Dagan, *Int. J. Infect. Dis.*, 2003,
7(Supplement 1), S21-S26

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

The examining division defined document (8) to be the closest prior art, in particular the sachet disclosed in Example 3 comprising amoxicillin and clavulanate in a ratio of 12:1 in a dry powder formulation for dissolution.

The examining division considered that the whole development illustrated by a number of prior art documents clearly showed a tendency towards increased amounts of amoxicillin relative to clavulanate, and that it was therefore within the normal routine of a skilled person to adapt the existing formulations in this direction to arrive at a ratio of 14:1, even in the case of paediatric patients.

The examining division did not consider that the post-published comparative data submitted supported an inventive step, since comparison had been made with formulations having a amoxicillin/clavulanate ratio of 7:1. Moreover, the examining division was of the opinion that the improvements demonstrated were not surprising in view of the greater amounts of amoxicillin used in order to achieve a ratio of 14:1

(i.e. 90/6.4 mg/kg/day) with respect to that chosen for comparison, namely, 45/6.4 mg/kg/day.

Hence, in the examining division's view, the subject-matter claimed in the main request lacked an inventive step.

The examining division further considered that the subject-matter of the first and second auxiliary requests lacked an inventive step for analogous reasons as set out for the main request.

IV. The appellant (applicant) lodged an appeal against this decision and filed grounds of appeal and further documents.

V. In two communications and in the communication sent as an annex to the summons to oral proceedings, the board *inter alia* expressed doubts as to whether the subject-matter of the requests on file were in conformity with the requirements of Articles 76(1), 123(2) and 84 EPC.

In addition, with the summons to oral proceedings, *inter alia* document (26) was introduced into the proceedings. This document was known to the board and to the appellant from the proceedings of the parent case (T0304/04-3302).

VI. With the letter of 22 June 2007, the appellant filed a new main (sole) request to replace the previous requests on file. Claim 1 of this request read as follows:

"1. A pharmaceutical formulation for paediatric dosing comprising amoxicillin and clavulanate which is in the form of a powder or granular product for reconstitution into a suspension or solution, such that the weight ratio of amoxicillin and clavulanate is 14:1."

In addition, the appellant requested that the case be remitted to the first instance (Article 111(1) EPC) in order to allow a proper consideration of the further documents introduced by the board with the summons to oral proceedings.

With the letter of 9 July 2007, the appellant filed additional document (28) as well as further arguments.

- VII. Oral proceedings were held before the board on 31 July 2007.
- VIII. Insofar as they are relevant to the present decision, the appellant's arguments presented at oral proceedings may be summarised as follows:

The appellant indicated that claim 1 of the main request related to a formulation adapted for paediatric administration, which had been developed to provide an empiric treatment in children of infections potentially caused by drug-resistant *Streptococcus pneumoniae* (DRSP), in particular respiratory tract infections such as otitis media.

The appellant disagreed with the examining division's choice of document (8) as closest prior art, which was driven by structural considerations only, without taking into account the problem addressed by

document (8), namely, the problem of maintaining amoxicillin in solution on reconstitution. Document (8) was totally silent on how any of the formulations described therein might be used, beyond the general use of treating bacterial infections.

The appellant submitted that document (26) provided a more realistic starting point for assessing inventive step since it disclosed formulations having the highest amoxicillin/clavulanate weight ratio, namely 8:1, to have been developed before the priority date for the same purpose as that of the present invention.

With respect to document (23), the appellant was of the opinion that this document was further removed from the present invention than document (26), since the former was concerned with the treatment of respiratory tract infections caused by DRSP rather than an empiric treatment thereof, and was not specifically directed to paediatric patients. In addition, the only amoxicillin/clavulanate formulation specifically exemplified therein was one with a weight ratio which was equivalent to a 4:1 in man (page 9, lines 17-21).

Starting from document (26) as closest prior art, the appellant referred to post-published document (28), which summarised data from documents previously filed, as providing evidence of an unexpected benefit of the present 14:1 formulation. The appellant pointed to Figure 3 disclosed in document (28) (page S25) as demonstrating that the 14:1 formulation was more effective against *S. pneumoniae* and significantly more effective against *H. influenzae* than the 7:1 formulation.

The appellant further argued that, even were the problem to be solved to be defined as lying in the provision of a further formulation comprising amoxicillin and clavulanate for the empiric treatment in paediatric patients of infections potentially caused by DRSP, an inventive step should nevertheless be acknowledged for the claimed subject-matter.

The appellant submitted that the paediatric suspension formulation having an amoxicillin/clavulanate weight ratio of 8:1 as disclosed in document (26) had been shown to provide an effective empiric treatment of acute otitis media (AOM) in infants. The appellant therefore concluded that there would be no motivation to further modify the 8:1 ratio, let alone to target the present ratio of 14:1.

With respect to document (23), the appellant contended that the teaching from this document as a whole was to use more clavulanate rather than less, which would lead to lower rather than higher ratios of amoxicillin to clavulanate. Thus, the skilled person would not have any motivation to explore higher ratios, and certainly not beyond the upper limit of 12:1 of the preferred range of 1:1 to 12:1 disclosed in document (23) for amoxicillin/clavulanate formulations.

No further arguments were added in respect of the appellant's request for remittal of the case to the first instance.

- IX. The appellant (applicant) requested 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 22 June 2007, and that the case be remitted to the first instance for further prosecution on the basis of said request.

Reasons for the Decision

1. The appeal is admissible.
2. Claim 1 of main and sole request
 - 2.1 The amendments introduced into claim 1 of the main request find their basis in the parent and divisional applications as originally filed (see page 2, line 11 - page 4, line 25 of respective descriptions).

Claim 1 of the main request therefore meets the requirements of Article 76(1) and 123(2) EPC.

- 2.2 Since none of the cited prior art documents disclose a pharmaceutical formulation comprising amoxicillin and clavulanate in a **weight ratio of 14:1**, the novelty of the subject-matter of present claim 1 can be acknowledged (Articles 52(1) and 54 EPC).

- 2.3 *Inventive step*

The board agrees with the appellant's analysis that document (26) represents the closest prior art.

This document relates to a clinical study into the treatment of AOM in patients aged three months to three years (see page 142, Summary, first sentence).

Pneumococcus is listed in the introduction as one of the most prevalent pathogens in AOM (page 143, left-hand column, third paragraph). The following paragraph in the introduction discloses the problem of recurrent AOM and the resulting increase in resistance to conventional antibiotics. The introduction then goes on to discuss the consequences of inappropriate treatment, and the fact Augmentin (i.e. a mixture of amoxicillin and clavulanate) has been conventionally used in a first-line treatment of AOM in infants (see page 143, right-hand column).

The oral paediatric drops studied in document (26) contain 100 mg of amoxicillin and 12.5 mg of clavulanate per millilitre (weight ratio 8:1), i.e. the same amounts of clavulanate as Augmentin and greater amounts of amoxicillin (page 144, left-hand column, third and fourth complete paragraphs).

The object of the study was to examine the therapeutic efficacy and tolerability of this paediatric formulation whereby the daily dosage of amoxicillin was 80 mg/kg/day administered three or four times a day. (page 144, left-hand column, last paragraph). It is noted that it is not explicitly stated in document (26) that the dosage of 80 mg/kg/day refers to the daily dosage of amoxicillin rather than to the total weight of formulation; however, this can be inferred from the content of document (26), since the daily dosage commonly used for the therapy of otitis is expressed in terms of the amount of amoxicillin prescribed (page 144, left-hand column, second complete paragraph).

The treatment disclosed in document (26) is empiric in the sense that the patients were not selected according to the nature or the susceptibility of the causative pathogens (see page 144, right-hand column, second to sixth paragraphs).

Document (26) concludes that the study confirms the effectiveness and safety of the new formulation (see page 143, right-hand column, last three sentences of Summary and page 147, right-hand column, "Conclusion").

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

The solution as defined in claim 1 relates to a formulation characterised by the fact that the weight ratio of amoxicillin to clavulanate is 14:1 and that the formulation is in the form of a powder or granular product, which is suitable for reconstitution into a suspension or solution.

It is noted that the feature "for paediatric dosing" appearing in claim 1 can only be understood to mean that the formulation has to be suitable for administration in paediatric patients. Since it is well known in the art that suspensions and solutions are suitable for paediatric dosing, this feature does not further limit the claimed subject-matter. This was not disputed by the appellant.

Having regard to the experimental results reported in example 3 of the present description, the board is satisfied that the problem has been plausibly 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 (26) discloses an oral paediatric formulation in the form of drops containing amoxycillin and clavulanate in a weight ratio of 8:1 as well as its use in the empiric treatment of AOM in infants.

When starting from this formulation, the skilled person working in the field of antibiotic therapy of respiratory tract infections and faced with the above-mentioned problem would be aware of document (23).

This document discloses the use of clavulanate in combination with β -lactam antibiotics, preferably amoxycillin, in 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 (23) discloses inter alia the treatment of otitis media and respiratory tract infections (see page 2, lines 17-24 and page 4, lines 2-14).

It is further disclosed in document (23) that, in view of the extreme moisture sensitivity of clavulanate, aqueous suspensions or solutions must be provided as dry solids for reconstitution with water shortly before administration (page 6, lines 17-29).

Therefore, it would be an obvious measure for the skilled person faced with the above-mentioned problem to provide the formulation in the form of a powder or granular product rather than in the form of the reconstituted solution or suspension.

As regards the possible ratios of clavulanate to antibacterial agent, document (23) discloses that this may vary 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 amoxicillin in a ratio range from 1:1 to 1:12 (page 7, lines 27-29).

Accordingly, the skilled person faced with the problem defined above is led by the teaching of document (23) to modify the proportions of antibacterial agent relative to clavulanate. Hence, the increase of the ratio of amoxicillin to clavulanate from 8:1 to 14:1 must be viewed as being an obvious modification within the teaching of document (23).

Consequently, the subject-matter of claim 1 of the main request lacks an inventive step (Articles 52(1) and 56 EPC) in view of the contents of documents (26) and (23).

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

2.4.1 It cannot be accepted that the claimed subject-matter plausibly solves the purported problem of providing an improved pharmaceutical formulation comprising amoxicillin and clavulanate:

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

The distinguishing feature of the subject-matter as claimed in present claim 1 relevant for the antibacterial effect is the weight ratio of amoxicillin to clavulanate of 14:1.

In the comparative data referred to by the appellant (see particularly document (28), page S25, Figure 3), an amoxicillin/clavulanate dosage regimen of 90/6.4 mg/kg (ratio 14:1) per day is compared with a dosage regimen of 45/6.4 mg/kg (ratio 7:1) per day. In other words, the ratio of amoxicillin to clavulanate is increased by doubling the daily dosage of amoxicillin and keeping the daily dosage of clavulanate constant.

Based on this evidence alone, it cannot be concluded that the ratio of amoxicillin to clavulanate of 14:1 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 amoxicillin to clavulanate to be increased by keeping the daily dosage of amoxicillin constant and decreasing the daily dosage of clavulanate, or with respect to the dosage regimen of 80/10 mg/kg per day disclosed in document (26).

2.4.2 The appellant's argument that the skilled person would not be motivated to modify the amoxicillin/clavulanate ratio of 8:1 disclosed in document (26) is also not convincing.

What the skilled person would be motivated to do depends on the problem that it wishes to solve. In the present case the problem to be solved is to provide further pharmaceutical formulations comprising amoxicillin and clavulanate. The prior art available to the skilled person is replete with examples of formulations containing amoxicillin and clavulanate in various proportions, as illustrated by documents (1), (8), (23) and (26). Hence, the skilled person would certainly consider such modifications as a solution to the above-mentioned problem.

2.4.3 With respect to the appellant's argument that the teaching of document (23) would dissuade the skilled person from going to amoxicillin to clavulanate ratios of greater than 12:1, it has to be noted that the teaching of document (23) is not confined to its preferred embodiments.

As outlined above, ratios of antibacterial agent to clavulanate are generally disclosed in document (23) to be from 30:1 to 1:1. Thus, the amount of clavulanate is taught in document (23) to be at most equal to **or much lower than** the amount of antibacterial agent.

Consequently, the fact that the preferred range disclosed in document (23) for the ratio of amoxicillin to clavulanate has an upper limit of 12:1 cannot be regarded as representing a prejudice that would

dissuade the skilled person from applying the more general teaching of document (23).

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

3. *Remittal*

With respect to the appellant's request for remittal to the department of first instance, it has to be remembered that the board has the discretionary power to decide on the remittal to the first instance (Article 111(1) EPC) after consideration of the merits of each case. There is no absolute right to two instances in the sense of a party being entitled in all circumstances to have every aspect of its case examined by two instances.

In the present case, there is a clear reference in document (1), which was already cited in the European Search Report drawn up for the present application, to the formulation of document (26): document (1) specifically looks forward to the availability of a paediatric formulation of Augmentin supplemented with extra amoxicillin to a dose of 80 mg/kg/day (page 554, right-hand column, third complete paragraph), i.e. the formulation disclosed in document (26). This was not disputed by the appellant.

The introduction of document (26) cannot therefore be regarded as having produced a "fresh case", since it merely complements the information of a document that was already present in the proceedings.

Thus, in view of the prior art already available in the examination procedure and the reasoning relied upon in the decision under appeal (cf. Summary of Facts and Submissions, point III), it is not to be expected that the examining division would reach a different conclusion as a result of the introduction of document (26). Therefore, remittal in the present case is unjustified since it would not serve any constructive purpose and would unnecessarily prolong the procedure.

Finally, it is noted, but not decisive, that the appellant was well aware of document (26) from the proceedings of the parent case (T0304/04-3302) and therefore cannot be said to have been taken by surprise by this document.

The request of the appellant in this respect is therefore refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald