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**Datasheet for the decision
of 19 March 2007**

Case Number: T 0304/04 - 3.3.02

Application Number: 96930817.0

Publication Number: 0862431

IPC: A61 K 31/43

Language of the proceedings: EN

Title of invention:

Use of a paediatric pharmaceutical formulation comprising amoxicillin and clavulanate

Patentee:

SMITHKLINE BEECHAM PLC

Opponents:

Grünenthal GmbH
Ranbaxy Laboratories Limited

Headword:

Use of a paediatric formulation comprising amoxicillin and clavulanate in the treatment of respiratory tract infections / SMITHKLINE BEECHAM

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main and auxiliary requests: inventive step (no), obvious combination of prior art teachings"

Decisions cited:

-

Catchword:

-



Case Number: T 0304/04 - 3.3.02

DECISION
of the Technical Board of Appeal 3.3.02
of 19 March 2007

Party as of right:
(Opponent 01)

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Decision under appeal:

Decision of the Opposition Division of the European Patent Office posted 23 December 2003 rejecting the opposition filed against European patent No. 0862431 pursuant to Article 102(2) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

- I. European patent No. 0 862 431, which was filed as international application WO 97/09042, was granted on the basis of six claims.

Independent claim 1 as granted read as follows:

"1. The use of amoxicillin and clavulanate in a nominal weight ratio of 14:1 in the manufacture of a medicament for oral administration to paediatric patients in the form of a powder or granular product for reconstitution into a suspension or solution suitable for being administered bid and at a dosage of 75 to 115 mg/kg amoxicillin per day and from 5 to 7.5 mg/kg of clavulanate per day for the treatment of respiratory tract infections."

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

- (2) WO 94/16696
- (4) S. Jacobsson et al, Eur. J. Clin. Microbiol. Infect. Dis., 1993, 12(5), 319-324
- (6) US-A-4 525 352
- (8) P.A. Todd, P. Benfield, Drugs, 1990, 39(2), 264-307
- (10) J. Astruc, Ann. Pédiatr., 1992, 39(2), 142-148
- (13) S. Baron, P. Bégué, Ann. Pédiatr., 1991, 38(8), 549-555
- (22) R. Dagan, et al, Pediatr. Infect. Dis. J., 2001, 20(9), 829-837

III. Oppositions were filed against the granted patent by opponents 1 and 2. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step and under Article 100(b) EPC for insufficiency of disclosure.

IV. The appeal lies from a decision of the opposition division rejecting the opposition under Article 102(2)EPC.

The opposition division considered that none of the grounds for opposition prejudiced the patent as granted.

In particular, the subject-matter of the claims as granted was considered to meet the requirements of novelty owing to the definition of the nominal weight ratio of amoxicillin to clavulanate as being 14:1.

With respect to the issue of inventive step, document (2) was considered by the opposition division to represent the closest prior art, which exemplified an amoxicillin to clavulanate ratio of 4:1. The problem to be solved was defined as lying in the provision of an empirical treatment of respiratory tract infections, particularly caused by DRSP (drug-resistant *Streptococcus pneumoniae*), in paediatric patients. The opposition division acknowledged inventive step based on the fact that it was not considered to be obvious that an increase in the amount of amoxicillin in an amoxicillin/clavulanate combination to a ratio of 14:1 would result in an improved paediatric formulation, as shown by the comparative example in the patent.

- V. The appellant (opponent 2) lodged an appeal against said decision and filed grounds of appeal together with additional documents.
- VI. In response, the respondent (patentee) filed a new main request and an auxiliary request, together with counterarguments and further documents.
- VII. Following a communication by the board, the respondent further filed additional documents and a new main request, which was subsequently amended to incorporate a minor correction with the letter of 12 March 2007.

The claims of the main request mainly differed from the claims as granted in that the daily dosage of amoxicillin in claim 1 had been limited to $90 \pm 10\%$ mg/kg per day and the dosage of clavulanate to $6.4 \pm 10\%$ mg/kg per day. As a result, dependent claim 6 as granted was redundant and was deleted. In addition, the phrase "suitable for being administered" had been replaced with the wording "for administration" in claim 1.

The auxiliary request previously filed with the letter of 23 September 2004 was maintained. This differed from the main request in that the daily dosage of amoxicillin had been restricted to 90 mg/kg and clavulanate to 6.4 mg/kg.

- VIII. Following the summons to oral proceedings sent on 2 November 2006, the appellant announced with the letter of 11 December 2006 that it would not be participating in and would not be represented at oral proceedings.

- IX. With the letter of 8 February 2007, the party as of right (opponent 1) announced that it would be attending but not participating in oral proceedings.
- X. Oral proceedings were held before the board on 19 March 2007.
- XI. The appellant's arguments were filed in writing with the grounds of appeal. They may be summarised as follows:

The objection raised under Article 100(b) EPC by opponent 1 during opposition proceedings was never pursued by the appellant.

The appellant no longer contested the novelty of the claimed subject-matter.

The appellant submitted that document (6) - read at the priority date of the opposed patent in the knowledge of the developments of amoxicillin-clavulanate paediatric formulations represented inter alia by documents (4), (8), (10), and (13), as well as the follow-up patent publication (2), and the medical practitioner's general knowledge - was an appropriate starting point to evaluate inventive step.

In the appellant's view, the problem to be solved was to provide a paediatric formulation with improved action against drug resistant bacteria and where there is an intermediate resistance, in particular for DRSP.

The appellant considered that the claimed solution to this problem was obvious in view of the above-mentioned prior art.

- XII. The respondent's arguments in respect of inventive step, insofar as they are relevant to the present decision, can be summarised as follows:

The respondent put forward that the purpose of the present invention lay in the development of an **empiric treatment** of respiratory tract infections in children, in particular where DRSP was suspected.

The respondent argued that, according to the established jurisprudence of the boards of appeal, the closest prior art was normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common.

The respondent considered document (2) to represent the closest prior art since it was concerned with the treatment of respiratory tract infections caused by DRSP by means of mixtures of amoxicillin and clavulanic acid, as illustrated by the experimental rat model corresponding to a dosage of 500 mg/125 mg (4:1 ratio) in man administered bid, i.e. twice daily (page 9, lines 15-21).

The respondent considered that document (10) was an inappropriate choice as the closest prior art since it did not address the issue of DRSP, but was rather concerned with β -lactamase mediated resistance and the

sequelae resulting from inappropriate treatment of acute otitis media (AOM), such as meningitis or bacteraemia. In this context, the respondent acknowledged that the earlier document (13) referred to the formulation as disclosed in document (10), but only in the context of pneumococci having intermediate rather than full resistance to penicillin.

The respondent further considered that, even were document (10) to be taken as the closest prior art, the claimed invention would involve an inventive step.

Having regard to document (10), the respondent defined the problem to be solved as lying in the provision of an alternative paediatric treatment for respiratory tract infections which was more convenient and potentially more efficacious.

The respondent referred to comparative data reported in the patent in suit and document (22) as demonstrating that this problem had been solved.

The respondent stressed that document (10) disclosed a regimen in which 80 mg/kg amoxicillin and 10 mg/kg clavulanate were administered three or four times a day, whereby this daily dosage was required in view of the risk of bacteraemia. It referred in particular to document (10), page 144, left-hand column, first complete paragraph.

The respondent argued that there was no teaching in the prior art of how to move to a more convenient (bid) paediatric dosing regimen without compromising efficacy.

In particular, the respondent argued that the skilled person would not be motivated to look to the teaching of document (2), which did not mention paediatric formulations. Moreover, the respondent considered that the only amoxicillin/clavulanate combination exemplified in document (2) was one which was equivalent to a 4:1 ratio in man, and that the teaching from the document as a whole was to use more clavulanate rather than less.

Similarly, the respondent argued that the skilled person would not have considered the teaching of document (4), since it only related to an amoxicillin to clavulanate ratio of 4:1 and did not address the issue of DRSP.

The respondent did not advance any additional arguments with respect to the auxiliary request.

XIII. The appellant (opponent 2) had requested in writing that the decision under appeal be set aside and that the patent be revoked.

The respondent (patentee) requested that the patent be maintained in amended form on the basis of the main request filed with the letter of 12 March 2007, or alternatively on the basis of the first auxiliary request filed with the letter of 23 September 2004.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123 EPC*

The amendments introduced into claims 1 of the main request and auxiliary request find their basis in the application as originally filed (see WO 97/09042, page 3, lines 30-35).

The amended claims 1 of the main request and auxiliary request have been restricted with respect to claim 1 of the granted version.

The amended requests therefore meet the requirements of Article 123(2) and (3) EPC.

3. *Novelty*

The novelty of the main request and auxiliary request has not been contested by the appellant and the board sees no reason to differ.

4. *Inventive step - main request*

4.1 Document (10) 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).

In the introduction, document (10) discloses that Augmentin (i.e. a mixture of amoxicillin and clavulanate) has been used in a first-line treatment of AOM in infants and that its spectrum of activity covers the majority of causative pathogens: H. influenzae, pneumococcus, Staphylococcus, Streptococcus A and

Branhamella catarrhalis (see page 143, right-hand column, last paragraph).

The new oral paediatric formulation studied in document (10) contains 100 mg amoxicillin and 12.5 mg of clavulanate per mL, 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).

Although it is not explicitly mentioned in document (10) that 80 mg/kg/day refers to the daily dosage of amoxicillin rather than to the total weight of formulation, this can be inferred from the content of the document, 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). This has not been disputed by the respondent.

Since the ratio of amoxicillin to clavulanate in the formulation of document (10) is 8:1, the daily dosage of clavulanate administered can be calculated to be 10 mg/kg.

The treatment disclosed in document (10) 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, paragraphs 2 to 6).

Document (10) concludes that this 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 and considering the fact that the subject-matter for which protection is sought relates to a Swiss-type form claim, the technical problem to be solved lies in the provision of a further empiric treatment of respiratory tract infections in paediatric patients using mixtures of amoxicillin and clavulanate.

The solution as defined in claim 1 of the main request relates to the choice of the daily dosage of amoxicillin as $90 \pm 10\%$ mg/kg and that of clavulanate as 6.4 ± 10 mg/kg in a ratio of 14:1, which is administered bid.

Having regard to the experimental results reported in example 2 of the patent in suit, 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.

Claim 1 of the main request specifies that a lower daily dosage of clavulanate is administered than that used in the treatment of document (10). This leads to a higher amoxicillin to clavulanate ratio.

However, the skilled person working in the field of antibiotic therapy of respiratory tract infections is aware of document (2), which discloses the use clavulanate in combination with β -lactam antibiotics such as amoxicillin in the treatment of bacterial infections caused by β -lactamase negative penicillin resistant pathogens such as *S. pneumoniae* and *H. influenzae* (in addition to some β -lactamase positive strains). In particular, document (2) discloses the treatment of otitis media and respiratory tract infections (see page 2, lines 17-24 and page 4, lines 2-14).

Concerning the dosage of clavulanate, document (2) states that "the clavulanate may suitably be administered to the patient at a daily dosage of from 0.3 to 15 mg/kg, preferably from 0.7 to 10 mg/kg, for example from 0.7 to 7 mg/kg, of body weight" (page 6, line 37 to page 7, line 1).

Thus, the daily dosages of clavulanate claimed in claim 1 fall within the preferred ranges recommended in document (2). Hence, the decrease in the amount of clavulanate administered from 10 to $6.4 \pm 10\%$ mg/kg per day must be viewed as being an obvious modification for the skilled person.

This conclusion is all the more true in view of the fact that it is well known that "the frequency of gastrointestinal adverse effects appears related to the dosage of clavulanic acid administered and may occur more often in children", as confirmed by the review

article document (8) (page 295, left-hand column, second paragraph of section 5).

As regards the frequency of administration, which is defined in claim 1 as being bid, the following has to be said: document (2) discloses administration of amoxycillin from 2 to 4 times daily as being equivalent alternatives (see page 7, lines 21-24).

Therefore, it would be an obvious measure for the skilled person faced with the above-mentioned problem to replace the tid regimen (i.e. thrice daily) known from document (10) with a bid regimen.

Additionally, the respondent has acknowledged that it was commonly known that the bid regimen is associated with better patient compliance than the tid regimen.

Consequently, the subject-matter of claim 1 of the main request lacks an inventive step (Article 56 EPC) in view of the contents of documents (10) and (2).

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

4.2.1 As regards the choice of closest prior art, it cannot be accepted that document (10) is not directed to the same purpose as the present invention. Although this document does not specifically mention the problem of DRSP, pneumococcus is listed in the introduction, third paragraph, as one of the most prevalent pathogens in AOM (page 143, left-hand column). The following paragraph in the introduction discloses the problem of recurrent AOM and the resulting increase in resistance

to conventional antibiotics, in particular owing to increasing percentage of β -lactamase-producing pathogens. The introduction then goes on to discuss the consequences of inappropriate treatment.

It is thus disclosed in document (10) that there is a problem of resistance in the target population and that the resistant strains are not limited to β -lactamase-producing pathogens. An effective empiric treatment would necessarily have to be capable of eradicating all resistant pathogens that are prevalent in the population, and the skilled person would be aware of the fact that this included DRSP.

This is confirmed by document (13), in which there is a clear reference to the formulation of document (10), as acknowledged by the respondent: document (13) looks forward to the availability of a paediatric formulation of Augmentin supplemented with extra amoxycillin to a dose of 80 mg/kg/day (page 554, right-hand column, third complete paragraph), i.e. the formulation disclosed in document (10).

This formulation is disclosed in document (13) as being useful in the treatment of AOM where intermediate resistant strains of pneumococci are suspected (page 554, right-hand column, third complete paragraph).

It has to be noted that although the text of document (13) refers to the fact that 12% of pneumococci are of intermediate resistance, the summary makes it clear that this figure is intended to include strains that are intermediate or resistant to

penicillin (see page 554, left-hand column, sixth paragraph and page 549, Summary).

Therefore, the purpose of the treatment disclosed in document (10) does not differ from the empiric treatment which is addressed in the patent in suit.

In contrast, document (2) does not specifically address the problem of empiric treatment of paediatric patients, but only generally discloses the treatment of respiratory tract infections caused by DRSP.

In relation to the dosage regimen, document (10) discloses a daily dosage and ratio of amoxicillin and clavulanate close to that reflected in the present claims, whereas the specific embodiment disclosed in document (2) is further removed both in terms of daily dosage and ratio of components (rats model on page 9, lines 15-21).

Hence, document (10) reflects a more realistic starting point for assessing inventive step.

- 4.2.2 The respondent's definition of the problem to be solved starting from document (10) as closest prior art cannot be accepted for the following reasons:

No evidence has been provided to make it plausible that the present dosage regimen is more efficacious than that disclosed in document (10). The only comparison disclosed in the patent in suit and in document (22) is between the dosage regimen according to the present claims of amoxicillin/clavulanate 90/6.4 mg/kg/day administered bid with a dosage regimen of

45/6.4 mg/kg/day administered bid (i.e. the amount of amoxicillin is halved and the amount of clavulanate is unchanged). No conclusion can be drawn from this comparative data about the relative merits of the present dosage regimen when compared to that disclosed in document (10), which discloses a dosage regimen of 80/10 mg/kg/day administered tid, i.e. wherein the amount of amoxicillin is equal to (or slightly lower than) and the amount of clavulanate lower than that claimed.

In addition, the problem as formulated by the respondent contains pointers to the solution, since, as outlined above, bid regimens are generally known to be "more convenient" than tid.

4.2.3 There is no reason why the skilled person would disregard document (2) when starting from the teaching of document (10). Although paediatric patients are not explicitly mentioned in document (2), it becomes clear from the description that the teaching is also intended to apply to this patient group, in particular, from the passage on page 6, line 37 to page 7, line 6. In the first sentence of this passage, daily dosages of clavulanate are given in mg/kg, which is typical for paediatric applications, since body weight adjusted doses are normally administered. In the following sentence, it is exemplified how the recommended values translate into a daily dosage regimen in an adult human (of approximately 70 kg body weight). It must clearly be inferred from this juxtaposition that the more general teaching is also intended to apply to children.

Concerning the respondent's argument that document (2) teaches that more clavulanate should be used rather than less, it has to be noted that the teaching of document (2) is not confined to its specific embodiments. The ratio of the amount of the clavulanate to the amount of antibacterial agent is disclosed to be from 1:1 to 1:30, i.e. the amount of the former is taught to be present in at most equal or much lower amounts than the latter (page 7, lines 12-17).

Furthermore, this is confirmed in the paragraph addressing preferred amoxicillin/clavulanate combinations (page 7, lines 27-33).

Consequently, the respondent's assessment of the teaching of document (2) as advocating greater amounts of clavulanate cannot be accepted.

- 4.2.4 It is a fact that the dosage regimen disclosed in document (10) requires administration three or four times a day (see page 144, left-hand column, last paragraph).

Although 2% of patients received only two doses per day, as listed in Table II, there is no further reference to this frequency of administration in the text.

However, the requirement in document (10) of administration three or four times daily does not represent a general prejudice that would dissuade the skilled person from applying the more general teaching of the later document (2) concerning the frequency of administration.

This is confirmed by further documents in this technical field, for instance, document (4), which was published approximately one year after document (10) and states in its introduction: "Over the last couple of years there has been a trend towards a decreased frequency in the dosage of oral antibiotics, and administration in a twice-daily dosage is now accepted practice in many countries for most oral antibiotics such as phenoxymethylpenicillin, amoxicillin and ampicillin. As amoxicillin is the antibacterially active component in amoxicillin/clavulanate, a b.i.d. dosage regimen should also be feasible with this combination" (page 319, right-hand column).

The children treated therein were selected for recurrent otitis media or failure of initial treatment of AOM (see document (4), page 319, abstract). Therefore, they were more likely to be carrying resistant pathogens.

Hence, there was no prejudice in the prior art against using a bid regimen of administration in the context of an empiric treatment where resistant strains may be implicated.

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

5. *Inventive step - auxiliary request*

The auxiliary request merely differs from the main request in that the daily dosage of amoxycillin is

restricted in claim 1 from $90 \pm 10\%$ to 90 mg/kg and clavulanate from $6.4 \pm 10\%$ to 6.4 mg/kg.

The assessment of inventive step presented under point 4 above therefore applies to the auxiliary request *mutatis mutandis*.

Additionally, the following has to be added: According to document (10), the daily dosage of amoxicillin commonly used for the therapy of otitis is 40 to 80 mg/kg, and even 100 mg/kg (page 144, left-hand column, second complete paragraph).

Therefore, the daily dosage of 90 mg/kg of amoxicillin as specified in claim 1 of the auxiliary request is within the range taught in document (10) to be tolerated in paediatric patients. Hence, the slight increase from 80 mg/kg as disclosed in document (10) to 90 mg/kg as claimed must be regarded as lying within the scope of conventional practice followed by the person skilled in the art.

The respondent did not advance any additional arguments in favour of the inventive step of this request.

Thus, the auxiliary request is rejected for lack of inventive step (Articles 52 and 56 EPC).

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:

A. Townend

U. Oswald