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Datasheet for the decision of 8 November 2012

Case Number: T 1760/08 - 3.3.02

Application Number: 97901052.7

Publication Number: 874631

IPC: A61K 31/52

Language of the proceedings: EN

Title of invention:
Use of valaciclovir for the manufacture of a medicament for the treatment of genital herpes by a single daily application

Patentee:
GLAXO GROUP LIMITED

Opponent:
Generics [UK] Limited

Headword:
Valaciclovir/GLAXO

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
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Keyword:
"Inventive step (no): obvious in view of a document of the state of the art"

Decisions cited:
G 0002/08

Catchword:
-

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Case Number: T 1760/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 8 November 2012

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 7 July 2008 revoking European patent No. 874631 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
R. Cramer

Summary of Facts and Submissions

I. European patent No. 0 874 631, based on international application No. PCT/EP1997/000192 published as WO 1997/025989 and having application No. 97 901 052.7 in the EPO, was granted with 8 claims.

Independent claim 1 as granted read as follows:

"Use of valaciclovir or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the suppression of recurrent genital herpes in a human host and for administration to said human host at a once daily dose of 200 mg to 1000 mg of the valaciclovir or the salt thereof."

II. Opposition was filed against the granted patent under Article 100(a) EPC (lack of novelty and inventive step), Article 100(b) EPC (added subject-matter) and Article 100(c) EPC (sufficiency of disclosure). Some arguments under these grounds were based on Article 52(4) EPC 1973.

The documents cited during the proceedings before the opposition division and the board of appeal include the following:

(1) WO 96/22291 A1

(2) WO 96/22082 A1

(5) R.J. Crooks, "Valaciclovir - a review of its potential in the management of genital herpes",

Antiviral Chemistry & Chemotherapy, vol. 6 (suppl. 1), 1995, 39-44

(8) S. Weller, "Pharmacokinetics of the acyclovir pro-drug valaciclovir after escalating single- and multiple-dose administration to normal volunteers", Clinical Pharmacology & Therapeutics, vol. 54, 1993, 595-605

(12) S.R. Mostow, "Suppression of recurrent genital herpes by single daily dosages of acyclovir", The American Journal of Medicine, vol. 85 (suppl. 2A), 1988, 30-33

(16) A. Mindel, "Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes", The Lancet, 1988, 926-928

III. By its decision pronounced at oral proceedings on 23 June 2008 and posted on 7 July 2008, the opposition division revoked the patent under Article 101(3)(b) EPC.

The opposition division first noted that the requirements of Article 123(2) EPC were fulfilled by the claims of the third auxiliary request remaining in the proceedings as the single request.

This request reads:

"Use of valaciclovir or a pharmaceutically acceptable salt thereof in the manufacture of a medicament **for oral administration** for the suppression of recurrent genital herpes in a human host and for administration to said human host at a once daily dose of **500 mg** of

the valaciclovir or the salt thereof." (addition to claim 1 as granted in bold).

Concerning Articles 54(2) and (3) the opposition division was of the opinion that the teaching of the patent in suit was anticipated by the teaching of neither document (1) nor document (2). Moreover, none of the documents cited during the opposition proceedings disclosed in combination all the features of the use of valaciclovir claimed in the patent in suit.

The opposition division, however, held that the subject-matter of this request did not meet the requirements of Article 56 EPC.

The closest prior art was document (5) relating to a clinical study in which valaciclovir was administered twice daily to increased numbers of patients in whom lesion development was prevented. Thus, virus suppression appeared to be indicated.

The problem to be solved was to find an alternative dosage regimen for the suppression of recurrent genital herpes.

With regard to the results of its example 12, the problem was solved by the teaching of the patent in suit.

Said solution, however, was obvious in view of document (12) on "Suppression of recurrent genital herpes by single daily dosages of acyclovir".

It was pointed out in documents (5) and (12) that once daily dosages were ideal for prophylaxis, so the particular dosage of 500 mg daily could be chosen by the skilled person without any inventive activity.

IV. The appellant lodged an appeal against that decision and filed grounds of appeal together with a request to maintain the patent according to the set of claims originally filed in the opposition proceedings as the third auxiliary request, the "main" request before the board (additionally annexed to the statement of grounds of appeal).

V. On 8 November 2012, oral proceedings took place before the board in the absence of representatives of the appellant and representatives of the opponent; duly summoned, both parties had informed the board in advance that they did not wish to attend.

VI. The appellant's submissions in writing may be summarised as follows:

Document (5) made no firm conclusions or recommendations on dosage frequency and amount of valaciclovir in long-term suppression therapy of herpes genitalis. In addition, considerations of the skilled person with regard to document (8) indicating the time-dependency of the plasma level of aciclovir would lead him to the conclusion that a once daily dosage would result in plasma levels declining within 10 to 12 hours to arrive at a level too low to produce any effect on herpes virus and thus would fail in suppression therapy of herpes genitalis. This view was endorsed by document (16) indicating that once daily administration

of acyclovir for suppression of herpes genitalis was not recommended.

VII. The respondent's arguments as filed in writing may be summarised as follows:

The opposition division was right in its decision on inventive step, in particular since the opposed patent did not disclose any results of clinical trials indicating unexpected advantages of the claimed dosage. It was shown only that 250 mg daily were not as efficient as 500 mg or 1000 mg daily, reflecting the normal behaviour of an active compound.

VIII. The appellant (patentee) had requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, filed with the grounds of appeal.

IX. The respondent (opponent) had requested in writing that the decision of the opposition division be maintained.

Reasons for the decision

1. The appeal is admissible.

2. *Claim 1 of the request; Articles 123(2) (100(c)) and 123(3) EPC, Articles 83 (100(b)) and 84 EPC; Article 54 EPC*

The board has no reason to disagree with the findings of the opposition division with respect to Articles 123(2) and 54 EPC.

Claim 1 of the request as amended with regard to claim 1 as granted has its basis in the application as filed in original claim 1, redrafted in second medical use format. Oral administration is disclosed as a preferred embodiment on page 5, lines 18-21 of the application as originally filed and all parts of the description are directed to oral dosage forms, in particular all examples and every specific disclosure in the overall text. The 500 mg dosage is disclosed as one of three embodiments in original claim 2 and on page 3, line 1.

The claim thus fulfils Article 123(2) EPC.

The opposition division's point of view with respect to the claimed dosage regimen is in line with the decision of the Enlarged Board of Appeal G 2/08, OJ EPO 2010, 456. Therefore, the board also does not deviate from the opposition division's conclusion on novelty.

By introducing of the amendments with regard to claim 1 as granted, the scope of the claim is narrowed. The requirements of Article 123(3) EPC are fulfilled.

Claim 1 of the request, relating to well-defined features such as a dosage of 500 mg or once daily administration, is clear and concise.

Based on these features, it can be carried out by the person skilled in the art.

Claim 1 of the request thus fulfils the requirements of Articles 84 and 83 EPC.

3. *Claim 1 of the request; Article 56 EPC*

3.1 The subject-matter of claim 1 of the patent in suit relates to the

(a) use of valaciclovir in the manufacture of a medicament
(b) for oral administration
(c) for the suppression of recurrent genital herpes in a human host
(d) at a once daily dose
(e) of 500 mg.

3.2 Document (5) represents the closest state of the art.

The disclosure of this document relates to the

(a) use of **aciclovir** in the manufacture of a medicament (see page 40, right-hand column, "Improvement opportunities", lines 7 to 9 together with line 2),
(b) for oral administration (*ibid*, lines 1 and 3)
(c) for the suppression of recurrent genital herpes in a human host (*ibid*, lines 8 and 9)
(d) at a **twice or four times daily** dose (*ibid*, line 9),

and discloses

– that there is another active compound that can replace aciclovir (see document (5), page 41, left-hand column, first paragraph under the heading "The potential of valaciclovir") because of its improved pharmacokinetic profile, with the result that for treatment of herpes zoster and genital herpes advances were achieved "with simpler thrice daily (zoster) and twice daily (genital herpes) oral

regimes compared with the five times daily dose frequency recommended for oral aciclovir, and without compromise to the excellent safety profile which characterizes aciclovir" (see document (5), page 43, left-hand column, second paragraph under the heading "Conclusion - a bright future") and

– that for treatment of herpes zoster instead of 800 mg aciclovir five times daily, 1000 mg valaciclovir was administered thrice daily (see document (5), page 41, right-hand column, third paragraph, last but one sentence) and for treatment of acute genital herpes instead of 200 mg aciclovir five times daily, 1000 or 500 mg valaciclovir twice daily was used (see document (5), page 42, right-hand column, second paragraph).

3.3 There is no evidence on the file of the patent in suit that the use of valaciclovir for administration to a human host at a once daily dose of **500 mg** according to amended claim 1 in suit exhibits an unexpected improvement over any dosage to be derived from the better bioavailability of valaciclovir. The dosage can be derived from the above-mentioned parallels and the recommended twice or four times daily administration of aciclovir for suppression of genital herpes given that, after oral administration, valaciclovir is readily absorbed and then undergoes almost complete (99%) hydrolysis to aciclovir (see document (5), page 41, right-hand column, second paragraph) such that the active substance after administration of valaciclovir is aciclovir anyhow.

Example 12 consequently indicates that administration of valaciclovir in a dosage of 250, 500 or 1000 mg once

daily shows better results with a rising amount of the compound. 500 mg is an arbitrary choice from these alternatives.

3.4 In the absence of evidence indicating a particular effect of the dosage of 500 mg, the problem to be solved has to be defined as

the provision of an alternative use of valaciclovir for the preparation of a medicament for oral administration for the suppression of recurrent genital herpes in a human host.

3.5 With regard to example 12 of the patent in suit, the board is satisfied that this problem is solved by the use of valaciclovir according to claim 1 of the main request.

3.6 In line with the overall aim of document (5) of reducing the frequency of administration (see also page 41, right-hand column, third paragraph, second sentence), it is outlined in context with suppression that it was "well recognised in medicine that, for prophylaxis, once daily regimens are optimal and ensure better compliance" (see *ibid*, page 40, right-hand column, last but one paragraph) and that the higher bioavailability of aciclovir from valaciclovir ensures that plasma aciclovir levels exceed the *in vitro* IC_{50} for clinical HSV (herpes simplex virus) strains with **once-** or twice daily dosing regimens (see *ibid*, page 39, left-hand column, "summary", second paragraph; the board's emphasis).

Thus, based on the recommended twice or four times daily administration of aciclovir for suppression of genital herpes from the state of the art, only a "frequency" of once daily administration of valaciclovir is to be derived for this suppression therapy from document (5).

The dose, as the single remaining feature of claim 1 of the request on file, can be determined from routine experiments without any inventive effort.

3.7 Consequently, the board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

4. Under these circumstances, the additional arguments of the appellant cannot hold.

As set out under point 3 of this decision, the teaching of document (5) establishes that valaciclovir would also allow reduction of administration frequency in suppression of herpes genitalis, given that figure 3 sets out "simulated plasma aciclovir concentration profiles following multiple oral doses of valaciclovir or aciclovir" taken from document (8). Therefore, the overall consequence of document (5) remains the same in view of the considerations on plasma levels of aciclovir according to document (8).

Even document (16) casts no doubt on the conclusions from the content of document (5), because it relates to aciclovir therapy (while document (5) starts from the new opportunities arising from the superior characteristics of valaciclovir) and because, even

there, a once daily therapy for suppression of herpes genitalis was not excluded but was set out as a possibility in particular circumstances (see document (16), page 928, left-hand column, second paragraph, last but one sentence).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald