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Datasheet for the decision of 30 October 2014

Case Number: T 1638/11 - 3.3.07

Application Number: 99956822.3

Publication Number: 1126826

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Language of the proceedings: EN

Title of invention:
MULTIPARTICULATE MODIFIED RELEASE COMPOSITION OF METHYLPHENIDATE

Patent Proprietor:
Alkermes Pharma Ireland Limited

Opponents:
Ferreccio, Rinaldo
LUDWIG, Gabriele

Headword:
MULTIPARTICULATE MODIFIED RELEASE COMPOSITION OF METHYLPHENIDATE/Alkermes Pharma Ireland Limited

Relevant legal provisions:
EPC Art. 100(b), 111(1)

Keyword:
Grounds for opposition - insufficiency of disclosure (no)
Appeal decision -
remittal to the department of first instance (yes)

Decisions cited:
T 1121/03, T 0369/05

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 1638/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 October 2014

Appellant: (Patent Proprietor)	Alkermes Pharma Ireland Limited Monksland, Athlone County Westmeath (IE)
Representative:	Ryan, Anne Mary Anne Ryan & Co. 60 Northumberland Road Ballsbridge Dublin 4 (IE)
Respondent: (Opponent 1)	Ferreccio, Rinaldo c/o Botti & Ferrari S.r.l. Via Locatelli 5 20124 Milano (IT)
Representative:	Ferreccio, Rinaldo Botti & Ferrari S.r.l. Via Cappellini, 11 20124 Milano (IT)
Respondent: (Opponent 2)	LUDWIG, Gabriele Nadistrasse 10 80809 München (DE)
Representative:	Isarpatent Patent- und Rechtsanwälte Friedrichstrasse 31 80801 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 May 2011 revoking European patent No. 1126826 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	R. Hauss
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 1 126 826 based on application No. 99 956 822.3 was granted on the basis of a set of 30 claims.

II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100 (a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, that the invention was not sufficiently disclosed, and that its subject-matter extended beyond the content of the application as filed.

III. The appeal by the patent proprietor lies from the decision of the opposition division to revoke the patent. The decision was based on the claims as granted as main request and five sets of claims filed with letter of 7 May 2010 as auxiliary requests 1-5.

IV. Independent claim 1 as granted read as follows:
"1. A multiparticulate modified release composition containing methylphenidate and having a first component comprising a first population of methylphenidate-containing particles and at least one subsequent component, each subsequent component comprising a subsequent population of methylphenidate-containing particles; wherein the at least one subsequent population of methylphenidate-containing particles further comprises a modified release coating or, alternatively or additionally, a modified release matrix material, such that the composition following oral delivery to a subject delivers the methylphenidate in a pulsatile manner, so as to produce periods of high blood plasma concentrations of methylphenidate interspersed with periods of low blood plasma concentrations of

methylphenidate, wherein the periods of low blood plasma concentrations provide wash-out of methylphenidate."

V. According to the decision under appeal:

(a) The requirements of Article 123(2) EPC were met by the main request.

(b) As regards sufficiency of disclosure of the main request, the opposition division took the view that it was common in the field of pharmacy to define a product by functional features, in particular of a plasma profile. The argument of the opponent, namely that plasma profiles differed substantially from one individual to another, had not been proven by technical evidence.

As regards the term "*wash-out*", no further definition apart from paragraph [0050] of the description could be found. According to this disclosure, any drop of the plasma profile after release of the first dose had to be considered as a "*wash-out*".

The curves A and B from Figure 1 provided several drops of the plasma concentration corresponding to the claimed "*wash-out*". It seemed however not plausible that the trough of curve A provided a wash-out able which could prevent the development of patient tolerance to methylphenidate. In conclusion, the skilled person would not know if the examples of the patent and corresponding plasma profiles A and B actually represented examples falling under the definition of claim 1. Since there was no example in the patent that clearly fell under the scope of claim 1, the skilled person had no starting point to put the invention into practice. The skilled person would have to test an indefinite number of possible

compositions to find out if these compositions showed a plasma profile as claimed.
The requirements of sufficient disclosure were not met by the main request.

(c) As the corresponding claims of all the auxiliary requests also contained the term "*wash-out*", the same conclusions applied.

VI. The patent proprietor (appellant) filed an appeal against the decision of the opposition division.
With the statement of grounds of appeal, the appellant filed two auxiliary requests and documents (24) to (27).

VII. With letter dated 9 May 2013, the appellant filed further data.

VIII. In a communication dated 30 September 2014 sent in preparation of oral proceedings, the board gave its preliminary opinion. In particular, it stated that the claimed invention appeared to be sufficiently disclosed.

IX. Oral proceedings took place on 30 October 2014.

X. The arguments of the appellant, as far as relevant for the present decision, may be summarised as follows:

The functional feature of claim 1 of the main request could not be interpretated independently from its corresponding structural features and was dependent on the structural features and the logical and inevitable consequence thereof.
The interpretation of Figure 1 of the patent on its own basis was not possible, since it had to be interpreted in the light of the examples. Figure 1 showed the release of methylphenidate from compositions comprising an immediate release component and a delayed release

component, and thus illustrated the high plasma concentrations corresponding to the release of each of the components comprising methylphenidate.
Each of curves A and B of figure 1 comprised a single "*wash-out*", which concept was defined in the description (see par. [0050]). The opposition division understanding that wash-out corresponded to any drop of the plasma profile after release of the first dose was technically incorrect. Since in cases A and B of Figure 1 only two populations of drug-releasing particles were present, only two peaks could be attained, and in consequence there would be only one trough between the peaks. The multiple dips observed in curves A and B of figure 1 were clearly artefacts in the plasma curve, but could certainly not be interpreted as "*wash-out*" periods.
As to the alleged technical effect of preventing the development of patient tolerance to methylphenidate, direct clinical evidence was not required in support of an effect which was plausible in the light of the disclosure of the specification. In said specification, there was a constant theme linking the pulsatile release profile and the reduction in patient tolerance.
Mimicking a sequential immediate release administration was advantageous in addressing tolerance.

XI. The arguments of the respondents (opponents 01 and 02), as far as relevant for the present decision, may be summarised as follows:

According to respondent 01, the skilled person was not provided with any information as to what constituted an acceptable level of wash-out, especially regarding its duration and the plasma level during that period.
Moreover, the term "*wash-out*" did not have a generally accepted meaning in the art.

The patent did not provide any disclosure as to how the lag time or time difference between the delivery from the first and second components could be varied, especially regarding the fact that claim 1 did not provide any restriction as to the nature of the first component.

The "*wash-out*" was supposed to reduce or prevent patient tolerance to methylphenidate, but this concept was not defined or quantified at any point in the patent specification, which did not disclose any clinical evidence or plausible support regarding this effect.

Figure 1 of the patent specification disclosed several drops of the plasma concentration, which appeared to be interpretable as several "*wash-outs*".

Curves A and B of Figure 1 of the patent specification did not include a trough which was low enough to cause a wash-out of the methylphenidate. Curve B of figure 1 was not representative of a composition according to the invention, since it did not mimic the release of two immediate release compositions given sequentially. Curve A of figure 1 did not show a plasma concentration drop as important as the control curve obtained with sequentially administered immediate release compositions.

The subject-matter of claim 1 was excessively broad, without any specification regarding the components, the release profile, the high and low plasma concentrations, and was defined only by unclear functional terms such as "*high*", "*low*" or "*wash-out*".

Only the subject-matter of dependent claim 12 referred specifically to a combination of immediate and modified release components.

The patent lacked sufficiency because the skilled person would not know in any given case, whether the desired amount of wash-out had been obtained, suitable for diminishing development of patient tolerance.

Additionally, according to respondent 02, the claimed *in vivo* parameters were not sufficiently disclosed, since no standard methodology of measurement existed. The *in vivo* measurements were also dependent on several factors not linked with the composition such as the physiological state of the patient, age or gender, and involved thus a great individual variability.
Even if the prevention of the development of patient tolerance was not expressed as a feature of claim 1, that effect could not be ignored in the assessment of sufficiency of disclosure, since it was presented in the teaching of the patent as closely linked with the wash-out feature.

XII. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case, based on the patent as granted, be remitted to the opposition division for consideration of the issues not previously heard at first instance.
In addition to the main request, the appellant had submitted two sets of claims as first and second auxiliary requests, with the statement setting out the grounds of appeal.

The respondents (opponents 1 and 2) requested that the appeal be dismissed.
Additionally, respondent 1 requested that documents (24) to (27) filed with the statement setting out the grounds of appeal and the data filed with the appellant's letter of 9 May 2013 not be admitted into the proceedings.

Reasons for the Decision

1. Main request - Sufficiency of disclosure

1.2 Claim 1 of the main request refers to a multiparticulate composition having a first component comprising methylphenidate-containing particles and at least a second component comprising methylphenidate-containing particles with a modified release coating or a modified release matrix material, such as to deliver methylphenidate in a pulsatile manner. Said pulsatile release is further defined in the claim by a functional feature namely "*so as to produce periods of high blood plasma concentrations of methylphenidate interdispersed with periods of low blood plasma concentrations of methylphenidate, wherein the periods of low blood plasma concentrations provide wash-out of methylphenidate*".
The claimed invention does not have any further restriction or specification as regards the nature of the first and second components, the pulsatile release, the intensity or duration of the high and low blood plasma concentrations periods and the corresponding "*wash-out*".
Accordingly, the skilled person must be taught by the patent specification how to provide the claimed multiparticulate compositions.

1.3 The components of the multiparticulate composition must be adapted to the object of the invention, namely the obtention of a pulsatile or multi-modal release. This release mode consists in producing a plasma profile substantially similar to the plasma profile produced by the administration of two or more immediate release dosage forms given sequentially (see par. [0014]-[0016] of patent specification). The components must thus be adapted to mimic such pulsatile release.

1.3.1 As regards the first component of the composition, the description of the contested patent specifies that it might be able to release a first portion of the active ingredient either immediately upon administration or after a delay time (see par. [0014], [0018], [0019], [0041]).
The second component is designed so that additional portions of methylphenidate are released after a lag time to provide additional pulses of drug release. Said second component may be a time-delayed immediate release or a time-delayed sustained release or extended release component in which the active ingredient is released in a controlled fashion over an extended period of time (see par. [0041]).
The combination of all possibilities for the first and second components is able to provide numerous release and plasma profiles (see par. [0042]).

Example 1 of the contested patent gives a specific embodiment of an immediate release particulate component of methylphenidate. This example provides further examples of modified release coating compositions to be coated over the immediate release particles and the dissolution data of the particles thus obtained in function of the coating level in weight gain of the basic immediate release particle (see table 3), while example 2 gives examples of modified release matrices. More than thirty different delayed or delayed-sustained release compositions and their *in vitro* dissolution profiles are thus given in example 1 (see Table 3) and in example 2 (see Table 5).
The skilled person would thus have no difficulty to combine either the disclosed immediate release particle with any of the disclosed delayed release or delayed-sustained release particles or any of the disclosed

delayed release particles together with another disclosed delayed release particle in order to provide a pulsatile delivery; the claimed combination is illustrated by several specific combinations of immediate release and delayed release particles and their pulsatile release profile is clearly illustrated by Figure 1 (see point (d) of example 1 and point (e) of example 2).
A large number of alternatives is therefore available to achieve the desired result of pulsatile release.

1.3.2 As to the further requirement defined by the functional feature "*so as to produce periods of high blood plasma concentrations of methylphenidate interdispersed with periods of low blood plasma concentrations of methylphenidate, wherein the periods of low blood plasma concentrations provide wash-out of methylphenidate*", it expresses nothing more than that the release profile must be multi-modal or pulsatile, and does not bring a further restriction to the object claimed by its structural features and its pulsatile release, especially given its broad definition.

1.4 Further arguments from the respondents

1.4.1 Sufficiency of disclosure was further objected to by the respondents with regard to the following specific points:

(a) The excessive broadness of the claim which amounted that the description of the patent in suit did not contain a technical concept fit for generalisation.
Thus, as in decisions T 1121/03 and T 369/05 cited by respondent 01, the functional definition given in claim 1 was no more than an invitation to perform a research programme in order to find the

suitable compositions. Hence, there was an undue burden in carrying out the invention throughout the whole area claimed.

(b) The use of unclear terms in the functional feature "*so as to produce periods of high blood plasma concentrations of methylphenidate interdispersed with periods of low blood plasma concentrations of methylphenidate, wherein the periods of low blood plasma concentrations provide wash-out of methylphenidate*"; in particular the term "*wash-out*" and the use of *in vivo* parameters rendered the preparation of compositions according to the invention impossible.

(c) The insufficient disclosure with regard to the reduction or prevention of patient tolerance which was linked, according to the patent in suit, with the administration of the claimed compositions.

(d) The deficiencies of Figure 1 and of the corresponding examples which were supposed to show a pulsatile release.

1.4.2 These arguments could not be followed by the Board:

(a) The circumstances underlying cases T 1121/03 and T 369/05 do not apply to present case.
The structural features for providing a pulsatile release and their disclosure in the description are as such self-sufficient to give the person skilled in the art enough information and technical guidance leading necessarily and directly towards success (see point 1.3.1 above). Moreover, the technical concept of the contested patent is illustrated by a large number of possible alternatives which makes it fit for generalisation, and this in itself only on the basis of the structural features of claim 1 of the

main request and their resulting pulsatile release.

(b) As to the point of the exact nature of the functional feature of claim 1 and its meaning, namely "*so as to produce periods of high blood plasma concentrations of methylphenidate interdispersed with periods of low blood plasma concentrations of methylphenidate, wherein the periods of low blood plasma concentrations provide wash-out of methylphenidate*", it appears that the terms "*periods of high blood plasma*", "*periods of low blood plasma*" or "*wash-out*" remain relative and cannot serve to give a clear definition of the claimed composition.

Moreover, a standardized and reliable method of *in vivo* measurement is absent from the claim and the measurement of *in vivo* parameters presents in general a great individual variability depending for instance on age, gender or weight.

The Board is however of the opinion that the ambiguity of the functional feature is not a matter to be addressed for insufficiency of disclosure but rather a question of Article 84 EPC, in view of the above-mentioned relative terms and individual variability.

(c) As to the question of tolerance, it is true that the claimed compositions were designed for reducing or preventing the develpment of patient tolerance as corollary of the pulsatile release (see par. [0003], [0017]).

This effect does however not appear in the claims which are only directed to compositions providing said pulsatile delivery. Its consideration for the assessment of sufficiency of disclosure is thus irrelevant.

(d) As to Figure 1, it shows the release profiles A and B of two compositions according to the invention. The presence of several artefacts of measurement in the curves does not occult the presence of two clear main peaks separated by a trough for each of the curves A and B, corresponding respectively to the release of the active agent from the two components of the composition and to the claimed "*periods of high blood plasma*" and "*periods of low blood plasma*", the latter providing said "*wash-out*". As demonstrated by these curves, in particular by curve B, the intensity and duration of the claimed periods and the trough can be variable, up to be discernible only with difficulty. This illustrates the wide range of possible pulsatile release profiles that fall under the scope of claim 1 of the main request.

1.5 Hence, the invention as defined in independent claim 1 of the main request can be performed by a person skilled in the art without undue burden.
Accordingly, the patent discloses the invention according to claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The requirements of sufficiency of disclosure are met and thus does not prejudice the maintenance of the patent as granted (Article 100(b) EPC).

2. Remittal to first instance

Although Article 111(1) EPC does not guarantee the parties an absolute right to have all the issues in the case considered by two instances, it is well recognised that any party should, whenever possible, be given the

opportunity to said consideration by two instances of the important elements of the case. The essential function of an appeal in inter partes proceedings is to consider whether the decision which has been issued by the first instance department is correct. Hence, a case is normally remitted if further opposition grounds have not yet been examined and decided by the department of first instance. This is the situation here.

Hence, the Board considers it appropriate to remit the case to the Opposition Division for further prosecution on the basis of the main request.

3. Since documents (24) to (27) and the data filed with letter dated 9 May 2013 were of no relevance to the Board's decision, it need not be decided whether they are to be admitted into the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution.

The Registrar: The Chairwoman:

S. Fabiani R. Hauss

Decision electronically authenticated