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Case Number: T 0962/20 - 3.3.07

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Language of the proceedings: EN

Title of invention:
FORMULATIONS OF MAZINDOL

Patent Proprietor:
Supernus Pharmaceuticals, Inc.

Opponent:
Regimbeau

Headword:
Mazindol/SUPERNUS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step (no) - obvious modification

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0962/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 November 2023

Appellant: (Patent Proprietor)	Supernus Pharmaceuticals, Inc. 1550 East Gude Drive Rockville, MD 20850 (US)
Representative:	Walcher, Armin Louis Pöhlau Lohrentz Patentanwälte Partnerschaft mbB Merianstraße 26 90409 Nürnberg (DE)
Respondent: (Opponent)	Regimbeau 20, rue de Chazelles 75847 Paris Cedex 17 (FR)
Representative:	Regimbeau 20, rue de Chazelles 75847 Paris Cedex 17 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 February 2020 revoking European patent No. 2552210 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	S. Ruhwinkel

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 2552210. The decision was based on the patent as granted (main request) and the claims of four auxiliary requests.

II. Claim 1 as granted read as follows:

"*1. A modified release formulation of mazindol comprising:*

a. mazindol as an active pharmaceutical ingredient,
b. at least one mazindol-containing component comprising a release controlling polymer selected from pH-dependent polymers and pH-independent polymers,
c. and a pharmaceutically acceptable low-moisture excipient, and wherein the total amount of water in the formulation is less than 2% by weight of the formulation,

wherein a first mazindol-containing component is an extended release component or a delayed release component and a second mazindol-containing component is an immediate release component, an extended release component, or a delayed release component, wherein each delayed release component comprises from 5% to 99% by weight of the formulation of at least one pH-dependent polymer and said extended release component comprises from 5% to 99% by weight of the formulation of a pH-independent polymer."

Claim 1 of auxiliary request I differed from claim 1 as granted in that it further specified that the modified release formulation "*comprises an osmotic core comprising mazindol and at least one pharmaceutically acceptable excipient, and a semipermeable rate-controlling membrane immediately surrounding said core*".

Claim 1 of auxiliary request II differed from claim 1 of auxiliary request I in that it further specified that "*said osmotic core is an osmotic tablet comprising a mixture of mazindol with osmotic agent(s), tabletting aides, and excipients*".

Claim 1 of auxiliary request III differed from claim 1 of auxiliary request II in that it provided a list of compounds from which the osmotic agents were to be selected.

Claim 1 of auxiliary request IV differed from claim 1 of auxiliary request III in that it specified that "*the mixture of mazindol, osmotic agent(s), tabletting aides, and excipients is tabletted either by direct compression or granulation followed by compression*".

III. The following documents cited by the parties during the opposition/appeal proceedings are referred to in the present decision:

D1	KR10-2007-0081903
D1a	English translation of D1
D2	US 2006/0240105 A1
D11	US 6,919,373 B1

IV. In the decision under appeal, the opposition division decided, among other things, that document D11 was

admitted into the proceedings and that none of the claim requests on file involved an inventive step starting from Example 3 of D1/D1a as the closest prior art.

V. The patent proprietor (appellant) filed an appeal against the decision. With its statement of grounds of appeal, the appellant re-filed the claims of auxiliary requests I to IV on which the decision was based.

VI. With its reply to the statement of grounds of appeal, the opponent (respondent) filed a new prior-art document.

VII. The board scheduled oral proceedings in line with the parties' requests and gave its preliminary opinion on the case.

VIII. Oral proceedings were held by videoconference, as requested by the parties. At the end of the oral proceedings, the board announced its decision.

IX. The appellant's arguments relevant to the present decision can be summarised as follows.

The formulation in claim 1 as granted was inventive. Starting from Example 3 of D1/D1a as the closest prior art, the formulation differed in that it contained components providing a modified release of mazindol, and in that its water content was below 2% by weight. Based on the technical effect produced by these differences, the objective technical problem was to provide of a mazindol modified-release formulation which avoided the instability caused by the presence of water.

D1a acknowledged the difficulties of preparing a delivery system for mazindol that worked effectively. Therefore, the skilled person had no reasonable expectation that a suitable mazindol formulation could be prepared. D1a did not give any information on the total amount of water that could be present in the formulation, a parameter that was decisive for the stability of mazindol.

D1a could not be combined with D2 because their contents were incompatible. D2 focused on methylphenidate and hydrocodone which, unlike mazindol, were not water-sensitive drugs. Paragraph [0081] of D2 disclosed a preparation step in which methylphenidate was dissolved in water. Such a step was contraindicated for mazindol, which was easily hydrolysed. The fact that methylphenidate and mazindol were indicated for the same therapeutic use was irrelevant and did not justify combining the two documents.

Claim 1 of auxiliary request I was further limited to an osmotic delivery system. As taught in paragraphs [0051] and [0058] of the patent, mazindol was stable in osmotic tablets and could be released at a rate that provided therapeutic serum levels for 6 to 24 hours. In view of the difficulties involved in formulating mazindol acknowledged in D1a, the skilled person was not provided with a pointer to the claimed delivery system. D1a could not be combined with D11 for the same reasons as it could not be combined with D2: D11 dealt with the formulation of methylphenidate, which was not a water-sensitive drug.

Claim 1 of auxiliary request II further specified that the core of the osmotic tablet comprised a mixture of mazindol with an osmotic agent, tabletting aids and

excipients. D11 did not suggest such a mixture since in its multi-layer osmotic tablets the osmotic agent and mazindol were contained in separate layers: the osmotic agent was in the push layer and mazindol in the drug layer.

The formulation in claim 1 of auxiliary request III was inventive because D11 did not suggest mixing mazindol with any of the osmotic agents listed in claim 1.

Claim 1 of auxiliary request IV involved an inventive step because the tabletting methods it proposed were carried out on a dry powder blend. These methods were particularly suitable for the formulation of mazindol, which was water sensitive. The preparation of multi-layer osmotic tablets in D11 was more cumbersome because it required compression of each layer separately and a subsequent compression to bring the layers together.

X. The respondent's arguments relevant to the present decision can be summarised as follows.

The formulation in claim 1 as granted was not inventive starting from Example 3 of D1/D1a as the closest prior art. D1a taught that mazindol formulations were greatly affected by their moisture content. This problem could be solved using an excipient with a loss on drying of 1% or less and an acid. In Example 3, mazindol was formulated using a dried excipient and an acid. The formulation mixture was dried until its loss on drying was lower than 1%, and then tabletted. This meant that the water content of the resulting tablets was less than 2% by weight. Therefore, the distinguishing feature between the formulation in claim 1 and the closest prior art was the presence of the mazindol-

containing components b. The technical effect produced by this difference was that the release profile of the formulation was extended or delayed.

The problem defined by the appellant was not credibly solved to the extent that it included the aspect of mazindol stability. Claim 1 did not contain features which, according to paragraphs [0050] and [0067] to [0071] of the patent, were essential for providing mazindol stability, namely an acidic excipient and the preparation method. Therefore, the objective technical problem was merely to provide a mazindol formulation with a modified release profile.

The solution proposed in claim 1 as granted was obvious in view of the common general knowledge or D2. The partial problem of the sensitivity of mazindol to moisture, if solved, had been dealt with in D1a by reducing the moisture content of the formulation to a minimum. D2 demonstrated that the solution proposed for the partial problem of preparing a modified-release formulation was obvious. D2 focused on methylphenidate, which had the same therapeutic use as mazindol. Whether or not the drugs in D2 were water sensitive did not matter for providing a modified release.

The limitation in claim 1 of auxiliary request I to an osmotic tablet did not overcome the lack of inventive step. For the reasons explained in relation to D2, D11 could also be combined with D1a. The formulations in D11 were the same as those disclosed in paragraphs [0056] and [0057] of the patent. D11 taught that osmotic tablets provided a constant release of methylphenidate for extended periods of time. A preferred embodiment, illustrated in Figure 2 and

Example 6, was a three-layer osmotic tablet coated with the active compound for initial immediate release.

The feature in claim 1 of auxiliary request II that the core of the osmotic tablet comprised a mixture of mazindol with osmotic agents, tabletting aids and excipents was obvious. This was the usual composition of an osmotic core, as taught in D11.

The formulation in claim 1 of auxiliary request III was also obvious. For instance, polyethylene oxide, which was one of the osmotic agents recited in claim 1, was present in the drug and push layers in the examples in D11.

Claim 1 of auxiliary request IV did not involve an inventive step because direct compression or granulation followed by compression were common processes for tabletting pharmaceutical formulations. Example 3 of D1a disclosed tabletting by direct compression.

XI. The parties' final requests relevant to this decision were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted. Alternatively, the appellant requested that the patent be maintained in amended form on the basis of one of auxiliary requests I to IV on which the decision under appeal was based.

- The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. Main request (patent as granted) - inventive step

1.1 The patent aims to provide stable formulations of mazindol, preferably modified-release formulations that provide therapeutic drug levels for 6 to 24 hours. Mazindol is an active compound that stimulates the central nervous system. It increases heart rate and blood pressure and decreases appetite. One problem with this compound is that it hydrolyses easily in the presence of water at alkaline pH. The patent proposes solving this problem by reducing the water content in the formulation to less than 2% by weight and using preferably acidic excipients. In addition, the formulation comprises two mazindol-containing components that provide a modified release of mazindol (patent, paragraphs [0003], [0010], [0021] and [0049], and claim 1).

1.2 The parties presented their inventive-step arguments starting from Example 3 of D1 as the closest prior art. As D1 is written in a non-EPO language, the parties relied on the English translation D1a. In the following, the board also refers to D1a as reflecting the content of D1.

Like the patent, D1a identifies the problem that mazindol is unstable in the presence of water at alkaline pH and aims to prepare mazindol formulations with enhanced stability (page 5, third and fourth paragraphs, and page 7, second paragraph). The experimental results in Tables 1 and 2 of D1a demonstrate that the stability of mazindol formulations

increases when their water content and pH value are reduced. Therefore, D1a proposes formulating mazindol with an excipient having a low water content (low loss on drying) and an acidifying agent. Example 3 of D1a illustrates the preparation of mazindol tablets containing corn starch as the low-moisture excipient and citric acid as the acidifying agent. Low-moisture corn starch and citric acid were mixed with mazindol and magnesium stearate, the mixture was dried at 80°C to have a loss on drying of 1% or less and then compressed into tablets. Table 3 of D1a sets out the stability of the formulation: after 21 days at 50°C and a relative humidity of 75%, the tablets in Example 3 lose only 1% of their initial mazindol content.

1.3 The parties did not dispute that the tablets in Example 3 of D1a provided immediate release of mazindol, which means that the formulation in claim 1 as granted differs in that it contains components that provide a modified release (feature b of claim 1); however, there was disagreement as to whether the total amount of water in claim 1, i.e. less than 2% by weight, constitutes an additional distinguishing feature. The appellant contested that the weight loss on drying of 1% or less of the mixture in Example 3 of D1a necessarily implies a total amount of water below 2% by weight.

The board concedes that it is difficult to establish the exact correspondence between the residual water content as defined in D1a and that in claim 1. Nevertheless, it is clear that the defined ranges overlap to a large extent and have the same purpose; both definitions aim to describe a minimum water content to lessen mazindol degradation. Therefore, even if claim 1 and D1a define the water content of the

formulation in different ways, their potential difference is not associated with any technical effect; the stability of mazindol can be considered to be comparable in both formulations.

Therefore, the technical effect associated with the formulation in claim 1 is the modified release of mazindol without impairing its chemical stability.

1.4 In view of this technical effect, the board accepts the objective technical problem as defined by the appellant, i.e. to provide of a mazindol modified-release formulation which avoids the instability caused by the presence of water.

1.5 The respondent considered (reply to the statement of grounds of appeal, pages 4 and 5) that the formulation in claim 1 did not solve this objective technical problem because the claim allegedly did not contain features which, according to the application as filed (paragraphs [0050] and [0067] to [0071]), were essential to ensure mazindol stability. These features were an acidic excipient and a particular preparation method.

In the board's view, the passages in the application as filed cited by the respondent teach that the presence of an acidic excipient and particular preparation methods are preferred rather than essential.

Paragraph [0050] states that a synergistic enhancement of mazindol stability is achieved by the combination of "*high-purity mazindol and low-moisture excipients, or low-moisture excipients and acidic excipients, or high-purity mazindol and low-moisture excipients and acidic excipients*". It is clear from this passage that low-

moisture excipients and acidic excipients contribute to mazindol stability and that their combination is desirable but not essential. The same conclusion can be drawn from paragraph [0067], which states that "*[s]tabilization techniques, such as using acidic pH media, for the drug substance would be required unless non-aqueous media are employed in the wet granulation process*".

With regard to the essentiality of a particular preparation method, the respondent referred to paragraphs [0066] and [0068] to [0071]. These passages do not support the respondent's allegation, either. The paragraphs refer to optimising mazindol stability and to operations that can be used or which are preferably used for preparing the claimed formulations. They do not disclose that such operations are essential to the invention.

The board holds that the formulation in claim 1 is a suitable solution to the problem posed.

1.6 With regard to the obviousness of the solution proposed in claim 1, the board agrees with the respondent and the decision under appeal (page 8, antepenultimate paragraph to page 9, first paragraph) that adapting the composition of the tablets in Example 3 of D1a to provide a modified release of mazindol is a customary measure in the field of pharmaceutical formulations. This is confirmed by D2 (abstract and paragraphs [0002] and [0017]), which discloses the preparation of multiparticulate modified-release formulations that deliver active compounds in a bimodal or multimodal manner. In paragraph [0073], D2 teaches that modified-release components can be prepared using generally known modified-release matrix materials or combinations

of them. Such materials e.g. include the pH-dependent polymer in claim 11 as granted, cellulose acetate phthalate, and the pH-independent polymers in claim 12 as granted, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, polyethylene oxide, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate and polyvinyl acetate. The broad range for the amount of these materials required by claim 1, i.e. 5 to 99% by weight, is obviously within the customary ranges.

With regard to the water content of the formulation, it was obvious from D1a that it had to be kept to a minimum to preserve mazindol stability. Therefore, the feature in claim 1 that the total amount of water in the formulation is less than 2% by weight, even if it is regarded as a distinguishing feature, does not involve an inventive step.

1.7 The appellant argued that the formulation in claim 1 was not obvious for two reasons. First, the skilled person had no reasonable expectation that a mazindol delivery system could be provided because page 4, penultimate paragraph, of D1a stated that it was difficult to prepare a formulation for delivering mazindol in such a way that it worked effectively. Second, the skilled person would not have combined D1a with D2 because the latter was directed to the formulation of active compounds that were not sensitive to water. The preparation process in paragraph [0081] of D2 was incompatible with mazindol because it required the active compound to be dissolved in water for particles to be coated with it.

These arguments fail. On the one hand, the passage on page 4, penultimate paragraph, of D1a is in the section discussing what was the prior art for D1a. The difficulty involved in formulating mazindol referred to in that passage was overcome by the invention in D1a, as demonstrated by the stability results presented in Table 3. On the other hand, D1a and D2 are not incompatible. D2 (abstract) is directed to the preparation of multiparticulate modified-release formulations in general. Its teaching is not limited to any particular drug, and there is no mention with regard to the water sensibility of drugs. Therefore, the skilled person had no reason to exclude water-sensitive drugs from the teaching of D2. The fact that paragraph [0081] of D2 discloses a coating step in which the active compound is dissolved is not incompatible with mazindol either. As noted by the respondent at the oral proceedings before the board, the coating step is carried out in one example and is not taught to be essential to the invention. Furthermore, the same operation is disclosed in the examples of the patent (paragraphs [0070], [0078] and [0100]).

1.8 In view of the above, the formulation in claim 1 as granted lacks an inventive step, and therefore does not meet the requirements of Article 56 EPC.

1.9 At the oral proceedings before the board, the parties also discussed inventive step in relation to the main request based on the combination of D1a with D11. For the reasons put forward below for auxiliary request I (point 2.3), the combination of D1a with D11 also renders the subject-matter of claim 1 as granted obvious.

2. Auxiliary request I - inventive step

2.1 Compared with claim 1 as granted, claim 1 of auxiliary request I contains an additional limitation to feature b, namely that the formulation comprises an osmotic core containing mazindol and at least one pharmaceutically acceptable excipient, and a semipermeable rate-controlling membrane immediately surrounding that core. This kind of formulation is generally known as an osmotic tablet. Osmotic tablets are controlled-release formulations; their core gradually absorbs water through the semipermeable membrane by osmosis, and the pressure generated in the core pushes the drug-containing material out at a controlled rate through one or several small holes drilled in the membrane.

2.2 This additional difference has the effect that the modified-release of mazindol occurs at a controlled rate and may provide therapeutic drug levels for an extended period of time (patent, paragraphs [0050] and [0058]). Therefore, the objective technical problem can be re-defined as that of preparing a formulation which provides therapeutic levels of mazindol for extended periods of time and avoids the instability caused by the presence of water.

2.3 The solution proposed in claim 1 was obvious in light of D11, which is directed to providing formulations that maintain the therapeutic effect of a drug over an extended period of time (column 1, lines 24 to 33). D11 explains that immediate-release formulations have the problem that they need to be administered at appropriate intervals to ensure sufficient drug concentration in blood, and that they produce undesirable fluctuations in drug levels (column 2,

lines 31 to 39). This problem was previously solved by delayed-release and sustained-release formulations, but these formulations do not always provide a constant release of the drug over extended periods of time (column 2, lines 45 to 55). In contrast, osmotic dosage forms are known to provide a constant release with the additional advantage that their operation is pH-independent and is not affected by the different environments in the gastrointestinal tract (column 3, lines 13 to 30). According to D11, maintaining a substantially constant rate of drug release for an extended period is particularly important for drugs which stimulate the central nervous system, e.g. when children suffering from ADHD are treated with methylphenidate (D11, column 6, lines 53 to 60 and column 7, lines 14 to 34). A preferred embodiment of D11 is an osmotic tablet with a three-layer core as depicted in Figure 2. Two layers of the core contain the drug along with selected excipients (drug layers) and the third layer contains an osmopolymer, optionally an osmotic agent, and selected excipients (push layer). The push layer absorbs water by osmosis and gradually pushes the drug layers out of the tablet providing a controlled release of the drug. In a more preferred embodiment, the three-layer osmotic tablet is coated with an immediate-release form of the drug (column 12, second paragraph; paragraph bridging columns 12 and 13; Figure 2). Such an osmotic tablet is illustrated in Example 6 of D11 and reflects a modified-release formulation as defined by feature b of claim 1.

The patent does not demonstrate that the formulation of mazindol in an osmotic tablet produces any technical effect beyond the controlled-release that characterises osmotic tablets. Consequently, in the light of D11, it was obvious to modify the tablet in Example 3 of D1a as

an osmotic tablet to obtain a formulation that provides therapeutic levels of mazindol for extended periods of time. Therefore, the formulation in claim 1 is not inventive (Article 56 EPC).

2.4 The appellant argued that the skilled person would not combine D1a with D11 because D11 deals with the formulation of methylphenidate, which, contrary to mazindol, is not sensitive to water.

This argument is not convincing. The teaching in D11 that osmotic tablets are known controlled-release formulations and that they provide constant drug levels for extended periods of time is not linked to a specific drug. The teaching is directed to drugs that need to be provided at constant rates, as is the case for methylphenidate for treating ADHD. This appears to also be the case for mazindol, according to the patent (paragraphs [0008] and [0010], and claim 17). Nothing in D11 suggests that osmotic tablets are not a suitable formulation for water-sensitive drugs.

3. Auxiliary request II - inventive step

Claim 1 of auxiliary request II further specifies that the osmotic core comprises a mixture of mazindol with osmotic agents, tabletting aids and excipients.

All these ingredients are well-known, basic ingredients of osmotic tablets. In multi-layer osmotic tablets at least the push layer must contain an osmotic agent (see D11, column 11, lines 53 to 59, and column 13, lines 1 to 8), but drug layers may also contain it. Column 3, lines 31 to 34 of D11 explicitly teach that the core of osmotic formulations contains the drug mixed with excipients and, optionally, osmotically active

components. With regard to tabletting aids, this is an ingredient generally used for preparing tablets. Consequently, the limitation in claim 1 of auxiliary request II amounts to a customary modification of the closest prior art.

Therefore, the subject-matter of claim 1 of auxiliary request II does not involve an inventive step (Article 56 EPC).

4. *Auxiliary request III - inventive step*

Claim 1 of auxiliary request III further specifies the osmotic agents that can be used in the formulation. The recited compounds appear to be standard osmotic agents. They were used, for instance, in the core of the osmotic tablets in Examples 1 to 6 and 9 of D11, which contain polyethylene oxide combined with sodium chloride or sorbitol. No evidence on file demonstrates that the osmotic agents listed in claim 1 produce a technical effect beyond their known behaviour as osmotic agents. Therefore, the formulation in claim 1 of auxiliary request III is not inventive (Article 56 EPC).

5. *Auxiliary request IV - inventive step*

Claim 1 of auxiliary request IV further specifies that the mixture of mazindol, osmotic agents, tabletting aids and excipients is tabletted either by direct compression or granulation followed by compression. According to the appellant, the compression methods in claim 1 are inventive because they do not require the use of water and prevent mazindol degradation. In addition, they do not require the compression of separate layers and final compression to bring all the

layers together, as in the multi-layer osmotic tablets in D11.

The board disagrees. As noted by the respondent, direct compression is a conventional tabletting method, and it was used to prepare the mazindol tablets in Example 3 in D1a. Furthermore, claim 1 encompasses multi-layer osmotic tablets (see also patent, paragraph [0056]), which means that preparing a formulation according to claim 1 is not necessarily simpler than preparing the formulations in D11. Therefore, the limitation introduced in claim 1 of auxiliary request IV cannot remedy the lack of inventive step of the previous claim requests (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated