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Datasheet for the decision of 25 January 2011

Case Number: T 0785/07 - 3.3.02

Application Number: 97922035.7

Publication Number: 0909171

IPC: A61K 31/22

Language of the proceedings: EN

Title of invention:
Use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine for increasing the levels of IGF-1

Patentee:
MENDES s.r.l., et al
Sigma-Tau Industrie

Opponent:
Lonza AG

Headword:
Increasing the levels of IGF-1/MENDES S.R.L.

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step - (no): Replacement of L-carnitine by its short chain esters obvious"

Decisions cited:
-

Catchword:
-

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Case Number: T 0785/07 **-** 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 25 January 2011

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 2 March 2007 concerning maintenance of European patent No. 0909171 in amended form.

Composition of the Board:

Chairman: U. Oswald
Members: A. Lindner
L. Bühler

Summary of Facts and Submissions

I. European patent No. 0 909 171 based on application No. 97 922 035.7 was granted on the basis of 6 claims.

The independent claims read as follows:

"1. Use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group comprising neuropathies of the optic nerve and of olfactory nerve, neuralgia of the trigeminal nerve, Bell's paralysis, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs; clinical syndrome of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensivity syndromes, obesity, and for cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, particularly of cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine.

6. Use of L-acetylcarnitine or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group comprising myasthenia and heart asthenia."

II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of

novelty and lack of inventive step, and under Article 100(b) EPC for insufficiency of disclosure.

III. The documents cited during the opposition and appeal proceedings included the following:

(6) US-A-5 240 961
(13) Exp. Neurol. (1994), 128, 103-114
(45) Int. J. Clin. Pharm. Res. (1992), XII(5/6), 299-304
(57) Drugs Exptl. Clin. Res. (1991), XVII(5), 277-282
(58) Bone (1990), 11, 397-400

IV. The present appeal lies from an interlocutory decision of the opposition division, pronounced on 15 December 2006, to maintain the patent in amended form on the basis of the main request filed during the oral proceedings before the opposition division. Claim 1 of the main request is identical to claim 1 as granted except for the deletion of Bell's paralysis and obesity from the list of diseases. Claim 6 is identical to claim 6 as granted except for the deletion of heart asthenia from the list of diseases.

V. The principal findings of the opposition division in the reasons for the decision posted on 2 March 2007 were as follows: deletion of some diseases from claim 1 did not contravene the requirements of Article 123(2) EPC, as the remaining diseases still comprised a list of considerable length. Deletion of the term "heart asthenia" from claim 6 as granted was also allowable under Article 123(2) EPC, as the resulting limitation to a particular disease amounted to a selection from a single list. Moreover, the subject-matter of the main

request met the requirements of Article 84 EPC, as the functional definition "for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1" was further defined by specific diseases. As for the ground of opposition according to Article 100(b) EPC, the opposition division concluded that the disclosure in paragraph [0003] in combination with examples 1 and 2 of the contested patent provided sufficient information for the skilled person to rework the invention without undue burden. Furthermore, the subject-matter of the main request was novel, as document (45) related to the treatment of Bell's disease which was not included in the list of diseases found in the claims.

As regards inventive step, document (6), which concerned the use of L-carnitine for increasing IGF-1 levels, was chosen as closest prior art. The problem to be solved was defined as the provision of alternative medicaments for the treatment of diseases resulting from low levels of IGF-1. The solution to this problem by replacement of L-carnitine by its acetyl-, isolvaleryl- or propionyl-esters was not obvious in that document (6) taught away from using these esters: thus, it was found in example 2 of document (6) that acetylcarnitine had an inhibitory effect on osteocalcin production, which would have dissuaded the skilled person from selecting this compound in view of the fact that there was a significant correlation between serum osteocalcin levels and IGF-1. Moreover, a comparison of example 2 of the contested patent with example 4 of document (6) revealed that acetylcarnitine effected an unexpected increase of IGF-1 as compared to L-carnitine.

VI. The appellant (opponent) lodged an appeal against that decision.

VII. With their reply to the statement of the grounds of appeal dated 20 November 2007, the respondents (patentees) filed a new main request. The independent claims read as follows:

"1. Use of L-acetylcarnitine, L-isovalerylcarnitine, L-propionylcarnitine or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group comprising neuropathies of the optic nerve and of olfactory nerve, neuralgia of the trigeminal nerve, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs, clinical syndrome of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensivity syndromes, for cicatrization of wounds, the treatment of burns, tissue regeneration, particularly of cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine.

2. Use of L-acetylcarnitine, L-isovalerylcarnitine, or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group comprising neuropathies of the optic nerve and of olfactory nerve, neuralgia of the trigeminal nerve, arthropathy, arthritis, cervical spondylosis and hernia of the intervertebral discs,

clinical syndrome of reduced height, cachexia and acute or chronic hepatic necrosis, Turner's syndrome, sarcopoenia, growth hormone insensivity syndromes, for cicatrization of wounds, the healing of ulcers, the treatment of burns, tissue regeneration, particularly of cutaneous, intestinal and hepatic tissue regeneration and the formation of dentine.

7. Use of L-acetylcarnitine or pharmacologically acceptable salts thereof for producing a pharmaceutical product for increasing the levels of IGF-1 for the therapeutic treatment or prophylaxis of cytological disorders or diseases related to IGF-1 selected from the group comprising myasthenia."

VIII. Oral proceedings were held before the board on 25 January 2011.

IX. In connection with inventive step, the appellant essentially argued as follows:

There were several possible approaches for inventive step. If document (6) was selected as closest prior art, the problem to be solved could be defined as the provision of alternative medicaments for the treatment of diseases resulting from low levels of IGF-1. In contrast to the finding of the opposition division in the decision under appeal, document (6) did not show that L-carnitine led to enhanced osteocalcin levels as compared to L-acetylcarnitine. The tests according to example 2 of document (6), on which this conclusion had been drawn, were insufficient for several reasons: firstly, the number of animals in the various groups was much too small. There were even groups comprising not

more than two animals. Furthermore, there were considerable uncertainties as far as the dosages were concerned. Thus, the footnote of table 2 indicated that "the actual amount of carnitine and derivatives consumed was estimated at only about half the indicated values especially at the higher dosage level where the feed had a more pronounced taste". As a consequence, the values were statistically not significant. In order to improve the statistical significance, it was reasonable to pool the values, i.e. to combine each pair having identical active agents but different amounts thereof to a single group. In doing so, one would arrive at the conclusion that L-acetylcarnitine effected a higher increase in osteocalcin concentration than L-carnitine. This finding was corroborated by the fact that L-acetylcarnitine led to an increase in osteocalcin concentration from six to twelve weeks, while the opposite was true for L-carnitine. Moreover, the appellant did not agree that IGF-1 could serve as a determinant of osteocalcin, as document (58), which had been cited by the respondents in this context, did not demonstrate a direct relationship between osteocalcin and IGF-1. If anything, document (58) showed an interdependence between the three compounds IGF-1, osteocalcin and vitamin D. Even this interdependence was contested in view of the fact that the linear relationships established in document (58) were very unusual in biological systems. Moreover, no surprising effect in terms of increased IGF-1 concentrations could be deduced from a comparison between example 4 of document (6) and example 2 of the contested patent, as the experimental conditions had been different and the values did not match at all and were therefore not comparable.

Alternatively, the claimed invention lacked an inventive step over further documents such as document (57), which disclosed the use of propionylcarnitine for the treatment of arterial and venous cutaneous ulcers.

X. In connection with inventive step, the respondents essentially argued as follows:

In contrast to the invention according to the present main request, document (6) did not relate to therapy but was concerned with reduced IGF-1 levels and bone loss associated with aging. It was evident from document (6) that aging was not a disease but an unavoidable physiological evolution which could involve physical disturbances such as adiposity, decrease of lean body mass and bone loss. Starting from document (6) as closest prior art, the technical problem to be solved concerned the provision of compounds capable of raising endogenous IGF-1 levels for achieving a therapeutic effect in diseases or cytological disorders caused by low levels of IGF-1. However, there was a technical prejudice in document (6) against using the short-chain carnitine esters for the purpose as claimed in the main request and this prejudice was based on four reasons. Firstly, as was mentioned in column 3, lines 15-21 of document (6), a critical function of carnitine consisted in the removal of toxic acyl groups from the mitochondria. Secondly, document (6) contained the information that short-chain carnitine esters were preferentially excreted, while free carnitine was reabsorbed by the kidneys. The skilled person would not select a substance as therapeutic agent which was immediately excreted. Thirdly, document (6) contained the teaching that a high E/F ratio was an indicator of

carnitine insufficiency indicating poor oxidation of fatty acids and low ATP production. The skilled person, trying to avoid a further increase of this ratio, had therefore an additional reason for not replacing carnitine by the specific short chain-esters. Lastly, document (6) clearly taught that there was a significant correlation between serum osteocalcin levels and IGF-1. Even if the skilled person was not interested in osteocalcin when trying to solve the problem defined above, he would take this link into consideration and therefore dismiss short-chain carnitine esters such as L-acetylcarnitine which inhibited osteocalcin formation. As regards the reliability of the figures in table 2 of document (6), there was no evidence in the form of expert declarations that they lacked statistical significance. Therefore, they must be taken into consideration. The appellant's reading of these data was not permissible, in particular as far as the pooling of groups with the same active agent in different concentrations was concerned, as the effect was dependent on drug concentration.

The further documents cited by the appellant were not pertinent, as none of them related to the increase of IGF-1 levels.

XI. The appellant requested that the decision under appeal be set aside and the European patent No. 0909171 be revoked.

The respondents requested that the patent be maintained on the basis of the main request filed with letter dated 20 November 2007.

Reasons for the Decision

1. The appeal is admissible.

2. Inventive step:

The present invention as defined by claim 1 relates to the treatment or prophylaxis of specific diseases susceptible to be treated by increasing the level of IGF-1 (see paragraphs [0001] and [0003] and claim 1 of the contested patent).

Document (6), which constitutes the closest prior art, concerns a method for treating reduced insulin-like growth factor levels (= reduced IGF-1 levels), and bone loss associated with aging, by administering L-carnitine. In the light of this prior art, the problem to be solved can be defined as the provision of further derivatives of L-carnitine for the treatment of diseases or disorders susceptible of being treated by increasing IGF-1 levels.

As a solution to this problem, the contested patent proposes the use as defined in present claim 1, in which L-acetylcarnitine, L-propionylcarnitine or L-isovaleryl-carnitine is used for producing a medicament for treating specific diseases or disorders related to IGF-1.

As for the question whether or not the problem defined above was indeed solved by the subject-matter of present claim 1, it is noted that the contested patent contains two examples which show that administration of L-acetylcarnitine effects increased concentrations of

IGF-1 in the serum. The contested patent does not, however, contain any tests demonstrating a successful treatment of any of the diseases or disorders figuring in claim 1. However, both the opponent and the patentee reasoned that the content of paragraph [0003] of the contested patent, which indicates that the diseases or disorders listed in present claim 1 can be prevented, cured or improved by administration of IGF-1, belonged to the common general knowledge at the effective filing date of the contested patent (see the first paragraph of point 3.3 of the reasons in the decision under appeal). This statement was reiterated by both parties at the oral proceedings before the board. Moreover, the respondents (then applicants) provided documentary evidence in the course of the examination procedure which did indeed show a connection between IGF-1 and the treatment of some of the diseases in question as well an animal study on Wistar rats demonstrating a beneficial effect of L-propionylcarnitine on wound healing (see applicant's letter dated 15 December 2003 and the evidence annexed thereto). Under these circumstances, and in view of the fact that the results obtained with L-acetylcarnitine in examples 1 and 2 of the contested patent can be extended to further short-chain esters of carnitine including L-propionyl- and L-isovaleryl-carnitine, the board is convinced that the problem defined above was plausibly solved.

The fact that the content of paragraph [0003] of the contested patent was common knowledge at the effective filing date of the contested patent means that the beneficial effect of IGF-1 on the diseases or disorders listed in present claim 1 cannot support an inventive step. Starting from document (6), it therefore has to be

evaluated whether or not it was obvious to replace L-carnitine by its acetyl-, propionyl- or isovalerylester in order to increase serum IGF-1 concentration.

For this evaluation, example 2 of document (6), which concerns an animal study in which the effect of L-carnitine, L-acetylcarnitine and γ-butyrobetaine on osteocalcin and serum L-carnitine concentration is examined, is of critical importance. At first sight, the data obtained by this study, which are summarised in table 2, appear to indicate that L-carnitine is superior to L-acetylcarnitine as regards osteocalcin concentrations. Both compounds are about equivalent as far as the concentration of serum L-carnitine is concerned. However, a closer look at the experimental conditions reveals that the data are not reliable for various reasons. Firstly, the number of individuals in each group is very small. Some groups (groups 3 and 5) comprise only two individuals, which means that the uncertainties as far as the statistical significance is concerned are considerable. Furthermore, the exact dosage is not known, as the mice consumed only part of the composition so that the amount of L-carnitine consumed had to be estimated (see the footnote of table 2). Moreover, table 2 does not disclose the osteocalcin and serum L-carnitine levels at the beginning of the assay (0 weeks) despite the fact that samples appear to have been taken (see column 9, lines 26-28). As a consequence, variations in the natural osteocalcin and serum L-carnitine levels between individual test animals are not taken account of in table 2. The test's lack of precision allows different conclusions to be drawn from the data of table 2 leading

to opposite results. Thus, a comparison between the osteocalcin levels for L-acetylcarnitine (50 mg/kg and 100 mg/kg) and the control after 6 and 12 weeks suggests that L-acetylcarnitine inhibits osteocalcin production, while table 2 at the same time discloses an increase in the osteocalcin level for 100 mg/kg L-acetylcarnitine from six weeks to twelve weeks, which indicates that L-acetylcarnitine stimulates osteocalcin production. Incidentally, the same result is obtained if groups 3 and 4 are pooled. In this context, it is noted that the respondents' objections to group pooling cannot be followed in view of the uncertainties concerning the exact quantities of active agent administered to the test animals (see footnote of table 2). As this problem concerns in particular the higher dosage level, a distinction between the two dosages 50 mg/kg and 100 mg/kg is not meaningful.

The board is aware of the further information in the footnote of table 2 indicating that some of the measured differences in terms of osteocalcin levels appear to be significant. However, in view of the numerous uncertainties and inaccuracies leading to different, even opposite, logical results, the board concludes that the data of example 2 of document (6) and any conclusions drawn from these data including the entire teaching with regard to L-acetylcarnitine must be disregarded and can therefore not be taken into consideration for the evaluation of inventive step. As a consequence of this conclusion, the question whether or not there is a correlation between osteocalcin and IGF-1 levels, which had been used by the respondents as a basis for an alleged prejudice against the use of L-acetylcarnitine on account of the data in table 2 of

document (6), is not relevant (see point X above, fourth reason for the technical prejudice).

Example 4 of document (6) shows that administration of L-carnitine effects an increase in both IGF-1 and serum L-carnitine (see table 4a). Document (6) also teaches that the ratio of free L-carnitine to esterified L-carnitine (E/F) is an important yardstick for the carnitine metabolism. A ratio E/F > 0.25 indicates an abnormal carnitine metabolism which is more frequently observed with aged patients and the oral administration of L-carnitine could stimulate the in vivo stimulation of IGF-1 (see column 11, lines 35-57).

In the light of this teaching, which associates a certain ratio E/F to the stimulation of the in vivo synthesis of IGF-1, it must be evaluated whether the skilled person, trying to solve the problem defined above and being aware that addition of L-carnitine esters might further increase the ratio E/F, has any incentive to choose the three short-chain esters according to present claim 1 or whether there existed a prejudice as alleged by the respondents (see point X above, third reason for the technical prejudice). The appellant contested the assertion that addition of L-carnitine esters had an increasing effect on the ratio E/F by arguing that L-carnitine was constantly esterified and deesterified in the human body so that it did not matter for the ratio E/F in which state - esterified or deesterified - the L-carnitine was administered. This argument is indeed supported by the teaching of document (13) which describes a study showing that long-term administration of L-acetyl-carnitine to senescent rats, which are characterised by

a loss of L-carnitine in the blood, in the CNS and in other peripheral tissues, restores L-carnitine concentrations to the values of healthy young animals (see lines 14-22 on the right-hand column of page 103). Restoration to the values of healthy young animals means that there is no abnormal ratio E/F > 0.25, from which the skilled person concludes that L-acetyl-carnitine is suitable for increasing L-carnitine levels in the serum and, as a direct consequence thereof, for increasing IGF-1 levels. Moreover, the skilled person also concludes from this study that there is no prejudice against the use of L-acetylcarnitine for reasons of toxicity or ineffectiveness due to rapid elimination from the body, as alleged by the respondents (see point X above, first and second reason for the technical prejudice). As a consequence, the subject-matter of the main and sole request does not meet the requirements of Article 56 EPC.

3. In view of this finding, an evaluation of the further objections raised by the appellant is not necessary.

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:

N. Maslin U. Oswald