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**Datasheet for the decision  
of 15 December 2010**

**Case Number:** T 0822/07 - 3.3.02

**Application Number:** 00982226.3

**Publication Number:** 1242094

**IPC:** A61K 31/57

**Language of the proceedings:** EN

**Title of invention:**

Methods for treating mild cognitive impairment

**Applicant:**

Corcept Therapeutics Inc.

**Headword:**

Glucocorticoid receptor antagonist for use in treating MCI /  
CORCEPT THERAPEUTICS INC.

**Relevant legal provisions:**

EPC Art. 83

**Relevant legal provisions (EPC 1973):**

-

**Keyword:**

"Sufficiency of disclosure (no): lack of sufficiency of  
disclosure in relation to the medical treatment specified by  
means of technical effects on a particular group of patients"

**Decisions cited:**

-

**Catchword:**

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Case Number: T 0822/07 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 15 December 2010

**Appellant:** Corcept Therapeutics Inc.  
(Applicant) Suite 100, 2500 Sandhill Road  
Menlo Park, CA 94025 (US)

**Representative:** Denison, Christopher Marcus  
Mewburn Ellis LLP  
33 Gutter Lane  
London EC2V 8AS (GB)

**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 8 November 2006  
refusing European patent application  
No. 00982226.3 pursuant to Article 97(1) EPC  
1973.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** M. C. Ortega Plaza  
L. Bühler

## Summary of Facts and Submissions

- I. European patent application No.00982226.3, was filed as international application WO 01/37840 with nineteen claims.
- II. The following documents cited during the proceedings are relevant for the present decision:
- (1) WO 99/59596
- (2) WO 99/17779
- III. The present appeal lies from a decision of the examining division refusing the application (Article 97(1) EPC 1973) for lack of inventive step (Article 56 EPC) of the subject-matter claimed in the main request vis-à-vis document (2), and on grounds pursuant to Article 52(2) EPC 1973.

Claim 1 of the request serving as basis for the examining division's decision read as follows:

1. The use of a therapeutically effective amount of a specific glucocorticoid receptor antagonist in the manufacture of a medicament for treating a patient with mild cognitive impairment who is 45 years or older and has normal levels of cortisol for a human population of that age, wherein the patient meets the following criteria:
  - (i) obtains at least one perfect score on the Folstein Mini Mental Status Exam in three administrations of said Exam;
  - (ii) receives a rating of 0.5 on the Clinical Dementia Rating Scale, and
  - (iii) scores 1.5 standard deviations or more below the age- and education-adjusted normal value on a paragraph recall test.

IV. The applicant (appellant) lodged an appeal against said decision and filed grounds thereto. With its grounds of appeal, the appellant maintained the request serving as basis for the examining division's decision as its sole request.

V. On 19 November 2009, the board issued a communication with an invitation to file observations under Rule 100(2) EPC.

In said communication the board recalled that the examining division never gave an opinion during the examination proceedings about Article 84 EPC for the amended claims, although the originally filed claims 1 to 13 (claims directed to a method of treatment in the international application WO 01/37840) were reworded as second medical use claims with the entry into the European regional phase. Moreover, the examining division's decision remained silent about the novelty (Article 54 EPC) of the subject-matter claimed in the use claims 1 to 13 vis-à-vis documents (1) and (2).

Consequently, the board informed the appellant that although the primary purpose of the appeal procedure is to give the losing party the possibility of challenging the decision under appeal as to its merits, the board had to exercise in the present case its discretionary power (Articles 111(1) and 114(1) EPC) and investigate the main request in relation to Articles 84, 83 and 54 EPC.

The Board raised objections within the meaning of Articles 84, 83 EPC, and Article 54(3) EPC vis-à-vis

document (1), for the subject-matter claimed in the request serving as basis for the examining division's decision.

VI. The appellant filed a substantive reply to the Board's communication with its letter dated 13 May 2010. It also filed as an annex thereto a "revised set of claims".

Claim 1 of the set of claims filed with the letter of 13 May 2010 read as follows:

1. A specific glucocorticoid receptor antagonist for use in treating mild cognitive impairment (MCI) in a patient suffering therefrom to prevent or slow further memory impairment, wherein the patient is 45 years or older and has normal levels of cortisol for a human population of that age, wherein the patient meets the following criteria:
  - (i) obtains at least one perfect score on the Folstein Mini Mental Status Exam in three administrations of said Exam;
  - (ii) receives a rating of 0.5 on the Clinical Dementia Rating Scale, and
  - (iii) scores 1.5 standard deviations or more below the age- and education-adjusted normal value on a paragraph recall test.

It also filed five additional post-published documents by other authors than the inventors of the application in suit.

VII. On 29 June 2010, the Board sent a communication within the meaning of Article 15(1) RPBA 2007 (which corresponds to Article 14(2) of the previous version of the RPBA) as an annex to the summons for oral proceedings.

In said communication the Board maintained its objections regarding Articles 84 and 83 EPC for the amended set of claims and gave reasons thereto.

VIII. The appellant filed *online* on 2 November 2010 a reply to the Board's communication sent as an annex to the summons for oral proceedings. It also filed an auxiliary request.

Claim 1 of the auxiliary request read as follows:

1. A specific glucocorticoid receptor antagonist for use in treating mild cognitive impairment (MCI) in a patient suffering therefrom to prevent or slow further memory impairment, wherein the patient is 45 years or older and has normal levels of cortisol for a human population of that age, wherein the patient meets the following criteria:

- (i) obtains at least one perfect score on the Folstein Mini Mental Status Exam in three administrations of said Exam;
- (ii) receives a rating of 0.5 on the Clinical Dementia Rating Scale, and
- (iii) scores 1.5 standard deviations or more below the age- and education-adjusted normal value on a paragraph recall test;

wherein the glucocorticoid receptor antagonist may be identified as such by the TAT assay, in which a compound can be identified as a glucocorticoid receptor antagonist when its administration decreases the amount of induced TAT activity as compared to a control: and wherein the glucocorticoid receptor antagonist exhibits at least 100-fold higher affinity for the glucocorticoid receptor than the mineralcorticoid receptor in a direct binding assay or a competitive binding assay in the presence of a known antagonist.

IX. Oral proceedings took place on 15 December 2010. During the oral proceedings the appellant withdrew the main

request filed with the letter of 13 May 2010 and filed an amended main request to replace it.

Claim 1 of the main request filed at the oral proceedings before the Board differed from claim 1 of the main request filed with the letter of 13 May 2010 as follows:

The word "specific" was deleted at the beginning of the claim, leaving the expression "glucocorticoid receptor antagonist", which was supplemented by its acronym "(GRA)", and the following definition was introduced at the end of the claim:

"; wherein the GRA preferentially binds to the GR rather than the mineralcorticoid receptor (MR) at a rate of at least 100-fold".

X. The appellant's arguments may be summarised as follows:

The appellant submitted that claim 1 was drafted as purpose-delimited medical use claim. Thus, the claim sought protection for the use of any thinkable (i.e. known and/or unknown substances) glucocorticoid receptor antagonist, which preferentially bound to the glucocorticoid receptor (GR) rather than to the mineralcorticoid receptor (MR) at a rate of at least 100-fold, for the treating mild cognitive impairment (MCI) in a particular group of patients. The specific subgroup of patients defined in the claim was suffering MCI, which was a disease on its own right.

Questioned by the Board, whether the treatment defined in claim 1 encompassed the treatment of MCI

independently from its cause, meaning that the treatment claimed also encompassed the treatment of patients who had suffered from a stroke (without diagnostic), or suffering an untreated diabetes condition, hormonal imbalance (brain fog) etc., the appellant answered positively and stated that a functional MCI may have all these different causes. However, MCI was a psychiatric and neurological disease entity since it was a symptomatic established condition with individual and identifiable symptoms. The appellant brought as an analogy the symptomatic treatment of a soared throat. It further stressed that the definitions for the patient subgroup included in the claim had to be fulfilled.

The appellant also submitted that the particular method defined in the claim was especially good in the defined subgroup of patients. Dementia patients were excluded. The appellant argued that only twenty years ago dementia patients were mixed up with patients suffering from MCI. It further argued that the patients to be treated had normal ranges of cortisol and that this prerequisite excluded patients suffering from Cushing's syndrome (independently from its origin) and patients with high levels of cortisol, at the moment of the treatment, caused by stress conditions.

The appellant also submitted that in the purpose-related product claim 1, the product was defined by functional terms. The functional definition "glucocorticoid receptor antagonist" (GRA) was an established definition on its own. At the time of filing of the application underlying the appeal the skilled person in the art had no difficulty in



appreciating what a GRA does. The particular structure of the GRA had no immediate relevance. It was the function that was important, i.e. that the substance hinders cortisol binding to the GR. At the time of the effective filing date of the application numerous GRAs were known and well established. The application provided sufficient information in this respect, and included citations to several patent literature about these compounds, which were available before the filing date. The skilled person would take any of these known GRA compounds and would know that it would have the function.

The appellant further contended that the application concerned a "break-through invention" and that claim 1 was not a reach-through claim, since the claim was not a compound "*per se*" claim looking for absolute product protection. The "invention" lay on the function of the substances for a particular use. There was a certain number of patents granted for medical uses in which the compounds were solely defined by their function. The conclusions reached in decision T 1063/06, OJ EPO, 2009, 516, did not apply to the present case. In the case underlying T 1063/06 the compounds to be used were themselves new compounds and they were defined by a new kind of research tool using a screening method set out in the description. In the present case the GR antagonism was well-established in the field at the effective filing date.

The appellant argued that according to decision T 292/85, OJ EPO, 1989, 275, the definition of the "invention" by functional terms was allowable even if the claim may generically embrace the use of unknown

compounds to be provided or invented in the future. It also cited decision T 68/85, OJ EPO, 1987, 228, and submitted that the nature of the "invention" and the contribution to the art were to be considered when assessing the requirements of Articles 84 and 83 EPC.

The appellant further submitted that the "invention" related to a function which was linked to the use claimed and that the function was adequately defined in the claim.

The appellant's additional argumentation was that there were two type of corticoid receptors in the brain the Glucocorticoid (GR) and the Mineralcorticoid (MR). The compounds as defined in claim 1 bound more preferably to GR than to MR, about a 100-fold. The MR was most of the time filled with cortisol, then the ideal was a drug which specifically blocked the GR. If the drug blocked both receptors then one had too many undesirable effects.

The board also asked the appellant to explain in how far there was sufficiency of disclosure and support in the description for the treatment of a patient subgroup which was defined, according to the lowest age limit as 45 years old, without any limitations regarding the causes or origins of the symptoms. The appellant answered that it was only natural that the choice of 45 years as the lowest limit for the age of the patients was arbitrary, but what was meant was to include young patients with diminished cognitive functions or cognitive decrease in earlier ages than the majority of patients suffering from MCI. The MCI in these younger patients was not necessarily the result

from stroke or diabetes, but the result from dysfunctional neuronal functions.

As regards the contribution to the art the appellant stated the following. It had been known that people show different responses to stress situations. For instance, two out of ten people from the army may present post-traumatic disorders, and eight out of ten don't and will continue with a normal life after having had similar traumatic experiences to the previous subgroup. This factual situation was also true for the development of depression. The response of people to stress was always different. The claim's wording clearly excluded those patients suffering from Cushing's syndrome and with high levels of cortisol. In analogy to the watering of plants which may reverse the effects of a lack of water in yellowing plants, but which comes too late for the burned out blackish specimens, the effect of the GRA was to prevent or slow further memory impairment in patients having normal levels of cortisol. After the present "invention" all the development in the field went in that sense. In fact, many patients can be helped by means of the "invention".

The appellant also argued that in the extreme case one could get this sort of impairment by giving extra cortisol to people. If one gives the cortisol then the subjects still show MCI four days after its administration. Excess of cortisol may harm cognitive functions (the appellant cited second paragraph on page 2 of the description). Therefore, one had to block cortisol activity reducing the effects of cortisol on

the GR at brain level for protecting from cognitive decrease and even for improving it.

The appellant also stated the following: "We know a group of patients with normal levels of cortisol, that for reasons we do not understand are vulnerable to the illness MCI" (it cited first paragraph on page 3). The gist of the "invention" is the fact that the antagonist blocks GR for its natural ligand. The present "invention" was like a "light-bulb invention", it came as a conclusion of observations in a variety of places in relation to the compound mifepristone, which is representative for the GRA group. That is the proof that the principle works.

Asked by the Board which parts of the description were to be considered for the disclosure of the general teaching the appellant referred to page 7, line 2, where it was taught to treat or ameliorate MCI with a GRA by blocking the interaction of cortisol with GR.

The appellant completed its arguments in relation to the main request by arguing that documents (1) and (2) were both applications generated by Dr Belanoff itself. Document (1) was a document within the meaning of Article 54(3) EPC. Both documents explored GR antagonists in the treatment of different psychiatric conditions. The skilled person was aware from document (2) that GR had already some function in this respect but there was no disclosure in document (2) about MCI. This prior art document gave the skilled person a certain level of knowledge but it neither anticipated nor rendered obvious the claimed "invention".

As regards the auxiliary request the appellant stated that the arguments submitted for the main request were valid *mutatis mutandis* for the auxiliary request. Moreover, the claim specified the TAT assay as the method for identifying the glucocorticoid receptor antagonist according to page 17 of the application. The assay referred to induced TAT activity as compared to a control. The control was normally either cortisol or dexamethasone, which was a well known agonist. One had to measure the TAT activity and see how to reduce it. This specification assisted the definition of the GRA and was a response to the board's objections in relation to the lack of a standard test. The TAT assay was the "universal" test for GR activity used worldwide and it was a standard test (well-established, well-known and generally accepted).

- XI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request filed during the oral proceedings, or, subsidiarily, on the basis of the auxiliary request filed with the letter of 2 November 2010.

## **Reasons for the Decision**

1. *Admissibility*
  - 1.1 The appeal is admissible.
  - 1.2 The amended main request filed at the oral proceedings before the board is admissible since it was a direct response to the discussion during the oral proceedings,

prior to its filing, and because the introduced amendments were clearly allowable under Article 123(2) EPC.

2. *Main request*

2.1 *Sufficiency of disclosure*

Article 83 EPC requires that the European patent application discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

It is to be reminded that the content of the whole patent application including the description and the examples, has to be investigated by the skilled person in the light of the general common knowledge of the technical field involved. It is the claimed "invention" which has to be investigated. The general legal principle is that the claims define the matter for which protection is sought and the examples illustrate specific ways of performing the invention.

As for the amount of technical detail needed for a sufficient disclosure, this is a matter which depends on an assessment of the facts of each particular case, such as the character of the technical field, and the actual technical detail disclosed.

The presently claimed "invention" is based on an alleged new and inventive medical use of an infinite number of compounds, which encompass known and unknown substances, defined by their function as a glucocorticoid receptor antagonist (GRA) (binding

preferably, by a factor of about 100-fold higher, to the glucocorticoid receptor (GR) rather than to the mineralcorticoid receptor (MR)). The medical use concerns the treatment of mild cognitive impairment (MCI) independently from its aetiology (except from the exclusion of Cushing's syndrome) in a particular patient subgroup which is characterised by including relatively young patients (45 years or older), not suffering from dementia (delimited in the claim by the criteria (i) to (iii)) and having normal levels of cortisol (for a population of that age). The technical effect specified in the claim is "to prevent or slow further memory impairment".

Thus, the "invention" claimed in the main request addresses the general principle that each and every GRA (binding preferentially to GR rather than to MR) is able to prevent or slow further memory impairment in the particular subgroup of patients defined in the claim, independently from the cause or origin of its cognitive impairment. Thus, there are two aspects to be investigated in relation to sufficiency of the claimed "invention" which concern the biochemical basis regarding the definition of the substance to be used as GRA (binding to GR rather than to MR) and the medical basis relating to the choice of a particular subgroup of patients to be successfully treated. These two aspects require sufficient disclosure for a credible functional link to the technical effect claimed, which is to prevent or slow further memory impairment in the particular group of patients.

An inspection of the description of the application as filed shows the following passages, which have been

cited by the appellant as a basis for the complete disclosure. In the general introduction, where the background is dealt with, it is stated: "Cortisol, which is secreted in response to ACTH (corticotropin), shows circadian rhythm variation, and further, is an important element in responsiveness to many physical and psychological stress. It has been proposed that, with age, the cortisol regulatory system becomes hyperactivated in some individuals, resulting in hypercortisolemia. It has additionally been postulated that high levels of cortisol are neurotoxic, particularly in the hippocampus, a brain structure that is thought to be central to the processing and temporary storage of complex information and memory" (page 2, second paragraph).

On page 3, first paragraph, it can be read: "There has been no evidence prior to this invention, however, that a glucocorticoid receptor antagonist can be an effective treatment for memory impairment in a mature population, especially in patients having cortisol levels that fall within a normal range". This statement is followed by further comments about patients in which the cortisol levels increase and about those "mature individuals who have experienced an aging-associated increase in basal cortisol levels" who "can have a level of glucocorticoid receptor activity that, with time, directly or indirectly results in impaired memory function". However, claim 1 of the main request addresses the treatment of young patients (45 years or older) with normal levels of cortisol for their age. Therefore, the mentioned passages of the description do not disclose the intended effects and functions claimed. Additionally, at the end of the first paragraph on



page 3, the compound RU486 (mifepristone) is identified as being one GRA which does not antagonise MR functions, and thus it is mentioned to be an appropriate substance for the use according to the "invention". However, further on page 3, lines 20-21, it is stated: "There have been no studies, however, that have shown that RU486 can improve memory function". The next paragraph on page 3 (lines 22-25) includes the mere statement that: "The present inventors have determined that glucocorticoid receptor antagonists such as RU486 are effective agents for specific treatment of age-associated memory impairment that is not affiliated with dementia in mature patients with normal cortisol levels". This statement has only a declaratory nature.

As regards the detailed description of the claimed "invention", the description does not contain any model disclosing the alleged improvements in memory function attained by the use of the GRA. Neither a model based on biochemical or pharmacological *in vitro* assays, nor an animal model showing any beneficial effects on memory for the GRA, can be found in the description. There is also no disclosure relating to any *in vivo* assays, or clinical assays, irrespective of the group of MCI patients to be treated. In particular, there is a lack of disclosure in relation to the intended technical effect for the subgroup of younger patients with normal cortisol levels defined in claim 1. The statements relating to the "selective" blockade of GR by the substance to be used, without affecting the MR in order to avoid undesirable effects, are insufficient for providing a clear and complete disclosure in relation to the claimed beneficial effects on memory

function in the intended medical treatment of the particular group of patients suffering from MCI.

In fact, the whole description is devoid of any data which could have served to fill the gap of an insufficient disclosure. Although part number 4, starting on page 19, is dedicated to "Treatment of MCI using the glucocorticoid receptor antagonists" it does not contain any specific information relating to the claimed "invention" but only refers to the general knowledge known in the pharmaceutical field for physically providing pharmaceutical formulations and dosage forms for medical use.

It has to be kept in mind that the claimed "invention" relates to a particular medical use linked to an intended technical effect for which sufficient support and disclosure should have been provided in the description.

The only passage cited by the appellant, when asked directly by the board during the oral proceedings, was the following: "In one embodiment, the methods of the invention use agents that act as GR antagonists, blocking the interaction of cortisol with GR, to treat or ameliorate MCI" (page 7, lines 1-2). This teaching is clearly insufficient for a clear and complete disclosure of the general principle claimed, which relates to the prevention of memory impairment, or retardation of further memory impairment, in MCI patients of 45 years (or older), independently from aetiology (apart from the exclusion of patients suffering from Cushing's syndrome) and which have **normal levels of cortisol for their age.**

Even if considering in favour of the appellant that the description of the application as filed establishes the existence of a link between high levels of cortisol and cognitive impairment, including memory function, in the light of which the suitability of using a GRA devoid of MR activity would appear plausible, there is still a lack of sufficiency of disclosure of the "invention" claimed. The claimed "invention" for which sufficient disclosure is lacking concerns the treatment of younger patients with normal cortisol levels, suffering mild cognitive impairment deriving from unknown causes. Moreover, there is a further lack of disclosure for the technical effect relating to a memory function improvement and/or preservation in those patients. In this respect the description rather invites the skilled person to perform a scientific research program than contains a complete disclosure of the "invention" within the sense of Article 83 EPC.

Therefore, the main request does not meet the requirements of Article 83 EPC.

Since the main request fails for lack of sufficiency of disclosure (Article 83 EPC) in relation to the medical treatment specified by means of the technical effect on a particular group of patients, it is not necessary to further investigate the broad functional definition given in claim 1, for identifying the compounds to be used, within the sense of Article 84 EPC (clarity and support in the description) and Article 83 EPC (in relation to the method for determining the GRA activity).

As regards the appellant's argument that the claimed invention is based on several observations in different places, unfortunately, these are not part of the content of the description.

Additionally, the argument that after the present "invention" all the development went in the sense predicted in the application, had been already answered with the board's communication sent on 29 June 2010. With said communication the board informed the appellant that, in view of the fact that the documents it had filed with its letter of 13 May 2010 have been published several years after the effective filing date of the application in suit (one of them more than nine years later), they could not serve as a basis for defining the knowledge of the skilled person at the time of the invention, nor could they be used to fill the gap of the specification in the application in suit in order to ensure a sufficient disclosure within the meaning of Article 83 EPC.

In relation to the alleged plausibility of the existence of a preventive beneficial effect on memory preservation owing to the hindrance of the binding of the natural ligand cortisol to GRs in the brain, a straight line should be drawn between the establishment of a scientific hypothesis or theory, which encourages scientific research to prove or disprove it, and the requirements for a clear and complete disclosure under Article 83 EPC justifying a broad patent protection, and its corresponding monopoly, for a particular medical use of an infinite number of compounds.

3. *Auxiliary request*

3.1 *Sufficiency of disclosure*

Claim 1 of the auxiliary request basically differs from claim 1 of the main request in that the method for identification of the glucocorticoid receptor antagonist has been defined in the claim as being the TAT assay, in accordance with page 17 of the description. This specification was undertaken in order to address an objection raised by the board during the written proceedings against the functional definition of the compound, given in claim 1 of the initially filed main request.

However, since the definition of the medical condition to be treated and of the technical effect to be achieved remain identical to those in claim 1 of the main request dealt with in the present decision, the arguments given for claim 1 of the main request apply *mutatis mutandis* to claim 1 of the auxiliary request.

Consequently, the auxiliary request also fails for lack of sufficiency of disclosure (Article 83 EPC).

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:

D. Meyfarth

U. Oswald