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**Datasheet for the decision
of 11 October 2010**

Case Number: T 0830/08 - 3.3.04

Application Number: 99928129.8

Publication Number: 1091759

IPC: A61K 45/06

Language of the proceedings: EN

Title of invention:

Composition for the induction of apoptosis in target cells

Applicant:

University of Dundee

Headword:

Rimcazole/DUNDEE

Relevant legal provisions:

EPC Art. 54, 56, 83, 84, 111(2), 123(2)

EPC R. 139

Keyword:

"Main request, auxiliary requests 1 and 2: clarity (no)"

"Auxiliary request 3: correction of an obvious error in
claim 4 (yes)"

"Added matter (no)"

"Clarity, sufficiency of disclosure, novelty, inventive step
(yes)"

"Remittal for adaptation of the description (yes)"

Decisions cited:

T 1048/98, T 0609/02, T 0903/05, T 0394/06, T 0391/07

Catchword:

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Case Number: T 0830/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 11 October 2010

Appellant: University of Dundee
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Representative: Sampson, Catherine
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 30 October 2007
refusing European application No. 99928129.8
pursuant to Article 97(1) EPC 1973.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
R. Gramaglia

Summary of Facts and Submissions

I. This is an appeal against the decision of the examining division dated 15 September 2006 refusing the European patent application No. 99 928 129.8 pursuant to Article 97(1) EPC 1973. The title of the application is "Composition for the induction of apoptosis in target cells".

II. The consolidated list of documents in these proceedings is as follows:

D1 WO 96/06863

D2 European Journal of Pharmacology, 1995, vol. 278, no. 2, pages 151-160, Brent, P.J. and Pang, G.T.

D3 CH 681 780

D4 Pharmacological Review, 1990, vol. 42, no. 4, pages 355-402, Walker, J.M. et al.

D5 Cancer Research, 1995, vol. 55, pages 408-413, Vilner, B.J. et al.

D6 Current Biology, 1997, vol. 7, no. 11, pages 860-869, Böttger, A. et al.

D7 Cell, 1995, vol. 83, pages 237-245, Hupp, T.R. et al.

D8 Journal of Cell Science, 1996, vol. 109, pages 1105-1112, Renzing, J. et al.

- D9 Molecular Biology of the Cell, 1995, vol. 6,
pages 1443-1458, Ishizaki, Y. et al.
- D10 Photochemistry and Photobiology, 1998, vol. 68(1),
pages 101-109, Separovic, D. et al.
- D11 Acta Haematologica, 1998, vol. 99, pages 138-147,
Nath, J. and Krishna, G.
- D12 Nature, 1997, vol. 388, pages 548-554, DiDonato,
J.A. et al.
- D13 Psychopharmacology, 1984, vol. 84, pages 282-284,
Chouinard, G. and Annable, L.
- D14 CNS Drug Review, 2004, vol. 10, no. 1, pages 1-22,
Gilmore, D.L. et al.
- D15 Experimental data - rimcazole activity against
normal and tumour cells - filed with letter dated
13 September 2010
- D16 European Journal of Pharmacology, 1993, vol. 242,
pages 209-211, Kamei, J. et al.
- III. The decision under appeal dealt with a main and five
auxiliary requests.
- IV. Independent claims 1 and 3 read of the main request
read:
- "1. Use of a sigma receptor ligand for the preparation
of a medicament for the treatment of cancer.

3. Use of a sigma receptor ligand for the preparation of a medicament for the preferential induction of apoptosis in a first population of cells compared to a second population of cells, wherein the cells of the first population are tumour cells."

The main request contained further:

(i) an independent claim 15 relating to a kit, (ii) a claim 2 dependent on claim 1 (iii) claims 4 to 14 relating to further embodiments of claims 1 and/or 3, and (iv) claims 16 to 18 dependent on claim 15.

In particular, dependent claims 11 and 12 read:

"11. The use of any one of claims 1 to 7, wherein the medicament further comprises an NFkB activating agent.

12. The use of any of claims 1 to 7, wherein the use further comprises employing p53 or an agent which causes overexpression or activation of p53."

V. The examining division held that

(a) claim 3 of the main request contravened the requirements of Articles 83 and 84 EPC because it did not recite a clear definition of a disease and therefore the claimed subject-matter could only be carried out with undue burden;

(b) claims 11 and 12 contravened the requirements of Articles 83 and 84 EPC because the structural characteristics of the functionally defined compounds "NFkB activating agent" and "agent which causes

overexpression of p53" were unclear and as a consequence the skilled person could not perform the stated function without undue burden;

(c) the subject-matter of claims 1 to 7 and 14 to 18 was not new in view of the disclosure in document D3;

(d) the subject-matter of claims 1 to 7 and 14 to 18 did not involve an inventive step in view of document D2 in combination with document D5 which both suggested the utility of sigma receptor ligands for cancer treatment. The examining division was not convinced by the appellant's argument that these documents did not disclose whether or not sigma receptor ligands damaged normal cells to an unacceptable extent in view of the fact that sigma receptor ligands such as rimcazole, haloperidol and pentazocine had been used as medicaments before.

- VI. All of auxiliary requests 1 to 5 were also unallowable because claim 1 of each lacked an inventive step.
- VII. With the statement of the grounds of appeal the appellant filed a main request, corresponding to the main request dealt with in the decision under appeal, and seven auxiliary requests.
- VIII. Oral proceedings were summoned to take place on 11 October 2010. In an annex to the summons the board informed the appellant of its preliminary opinion that the disclosure in documents D2 and D5 suggested a possible use of sigma receptor ligands for the treatment of cancer. As to the appellant's argument that the extrapolation from the cell culture

experiments with rimcazole disclosed in document D2 would reveal that an unrealistically high dose would be needed for the treatment of humans, the board noted that the same did not necessarily apply for other sigma receptor binding compounds. Therefore, the result obtained for rimcazole would not deter the skilled person from considering other known sigma receptor ligands to be useful anti-cancer drugs.

- IX. In reply the appellant filed new auxiliary requests 8 to 10 and document D15 and notified the board that the main request and auxiliary requests 1 to 6 were withdrawn.
- X. In a letter dated 30 September 2010 the appellant announced that it would not attend the oral proceedings.
- XI. In a communication dated 4 October 2010 the board informed the appellant that in view of their limitation to the use of rimcazole the claims of the requests under consideration, i.e. auxiliary requests 7 to 10, fulfilled the requirements of Articles 54, 56 and 83 EPC. However, each of these requests suffered from formal deficiencies. For example, claim 13 of auxiliary requests 8 and 9 was unclear in the in the light of their claim 14.
- XII. In reply with a letter received by the board on 6 October 2010 the appellant filed a main request - corresponding to the previous auxiliary request 7 - and auxiliary requests 1 to 3 - corresponding to the previous auxiliary requests 8 to 10 as well as new auxiliary requests 4 and 5 and amended pages 18, 19 and 25 to 30 of the description.

Independent claim 3 of the **main request** read:

"3. Use of rimcazole for the preparation of a medicament for the preferential induction of apoptosis in a first population of cells compared to a second population of cells, wherein the cells of the first population are tumour cells."

Claims 13 and 14 of **auxiliary requests 1 and 2** read:

"13. A kit comprising:

(a) a composition comprising a sigma receptor ligand as defined in claim 1 in a pharmaceutically acceptable carrier; and

(b) directions instructing administration of the composition in a manner which would result in the preferential induction of apoptosis in a first population of cells compared to a second population of cells, wherein the cells of the first population are tumour cells and the cells of the second population are non-tumour cells.

14. The kit of claim 13 wherein the kit is for the treatment of cancer."

The only independent claim of **auxiliary request 3**, claim 1 read:

"1. Use of rimcazole for the preparation of a medicament for the treatment of cancer."

The request moreover had six claims dependent on claim 1. Claims 4, 6 and 7 of them read:

"4. The use of any of the claims 1 to 3, wherein the medicament further comprises a second sigma receptor ligand, which ligand is haloperidol, reduced haloperidol, rimcazole, [and 32 further compounds or groups of compounds](unnecessary text omitted by the board).

6. The use of any one of claims 1 to 3, wherein the medicament further comprises an NFkB activating agent as defined in Table 1.

7. The use of any one of claims 1 to 3, wherein the use further comprises employing p53 or an agent which causes overexpression and/or activation of p53, wherein the agent is a p53 expression vector, etoposide or gamma radiation."

XIII. Thus, the appellant's requests derivable from its submission of 6 October 2010 was that the decision under appeal be set aside and that a patent be granted on the basis of the main request or one of auxiliary requests 1 to 5 and the amended description, all filed with the letter of 6 October 2010.

XIV. In a further communication dated 7 October 2010 the board drew the appellant's attention inter alia to the fact that (a) in those dependent claims of the newly filed requests relating to the use of a second sigma receptor ligand the word "rimcazole" had apparently not been deleted by oversight and that therefore, if appropriate, a reasoned request for correction under

Rule 139 EPC should be received before the oral proceedings and that (b) the board considered it adequate, should the claims of one of the requests be found allowable, to remit the case to the first instance with the order to grant a patent on the basis of those claims and a description to be adapted thereto, since the proposed amended description had been filed too late for consideration at the oral proceedings.

- XV. Oral proceedings were held on Monday, 11 October 2010. Nobody appeared on behalf of the appellant.
- XVI. Since a request for correction as mentioned in the board's communication of 7 October 2010 was not in its hands at the beginning of the oral proceedings, the board adjourned the oral proceedings in order to contact the appellant's representative by telephone via the board's registrar to verify whether or not the representative had reacted to the board's communication of 7 October 2010.
- XVII. Subsequently, the board received a letter by telefax in which the appellant requested the correction of an obvious error, i.e. the deletion of the word "rimcazole" in claim 7 of auxiliary request 4. During a further telephone conversation with the board's registrar the appellant's representative confirmed that she would agree that the request under Rule 139 EPC also referred to claim 4 of auxiliary request 3 instead of to claim 7 of auxiliary request 4.
- XVIII. The oral proceedings were then resumed. At their end the board announced its decision.

XIX. The appellant's arguments submitted in writing were as follows:

Main request

Article 84 EPC

Claim 3 was clearly directed to the treatment of cancer as it recited "wherein the cells of the first population are tumour cells".

Auxiliary requests 1 and 2

Article 84 EPC

Claim 13 in both requests clearly referred to the treatment of cancer since it recited that the first population of cells were tumour and the second population were non-tumour cells.

Auxiliary request 3

Correction of an obvious error

Claim 1 of auxiliary request 3 related to the use of rimcazole. Claim 4 of that request depended on claim 1 and specified that a "second sigma receptor ligand" was present in the medicament. The list in the claim of possible "second sigma receptor ligands" recited rimcazole. However, since according to claim 1 rimcazole was already present in the medicament, the same compound could not constitute a "second" sigma receptor ligand. Hence, the reference in claim 4 to rimcazole was an obvious error and should be corrected according to Rule 139 EPC.

Articles 83 and 84 EPC

None of the claims of auxiliary request 3 recited the expression "preferential induction of apoptosis in a first population of cells compared to a second population of cells, wherein the cells of the first population are tumour cells". Therefore, there was no lack of clarity and/or sufficiency of disclosure in this respect.

In claim 6 the meaning of the term "NfκB activating agent" was clear because the skilled person knew compounds fulfilling the indicated function or could determine such compounds by straightforward and well-known tests. As to the feature "agent which causes overexpression of p53" in claim 7, no lack of clarity arose because these agents were specifically mentioned in the claim. Therefore, also no undue burden was involved when carrying out the invention claimed in claims 6 and 7.

Novelty

Document D3 did not mention rimcazole at all. Since the present claims related specifically to the use of rimcazole in the treatment of cancer, document D3 did not take away their novelty.

Inventive step

The problem to be solved was the provision of a treatment for cancer and the solution was to use rimcazole.

Example 10 was evidence that the application solved this problem in that it showed that rimcazole reversed the growth of tumour explants in mice with no deleterious side effects.

Document D2 showed that the sigma receptor ligands haloperidol, reduced haloperidol, DTG, SKF10047, (+) and (-) pentazocine and rimcazole inhibited the proliferation of human mammary and colon carcinoma and melanoma cells in culture. Thus, the document showed some role of sigma receptor sites in tumour cell biology. However, in the case of rimcazole document D2 disclosed that the concentration of drug required to induce cell death in cell culture was at least 25 μ M. The skilled person would conclude from this concentration that, to be effective in the treatment of cancer in human beings, very high concentrations of rimcazole had to be administered, i.e. in the order of 34.8 g/day. Rimcazole had originally been developed as an anti-psychotic agent. It was known, for example, from document D13, that daily doses of 500 mg caused seizures. Thus, unacceptable side effects were to be expected from the necessary dosage and the large amount of rimcazole would certainly not be reconcilable with patient compliance.

Thus, the claimed subject-matter was not obvious.

Reasons for the decision

Main request

Article 84 EPC

1. Article 84 EPC stipulates inter alia that the claims shall be clear.
2. The meaning of a claim is determined from the skilled person's point of view reading the claim with his/her background knowledge in the context of all of the claims and the whole specification.
3. Claim 3 relates to the "[u]se of rimcazole for the preparation of a medicament for the preferential induction of apoptosis in a first population of cells compared to a second population of cells wherein the cells of the first population are tumour cells".
4. A claim directed to a second medical use is considered as clear only if the disease to be treated is clearly defined in it (for example decision T 1048/98, points 2.1 to 2.5 of the reasons). In the present case the disease to be treated is defined in functional terms as "the preferential induction of apoptosis in a first population of cells compared to a second population of cells wherein the cells of the first population are tumour cells". The question is whether or not the skilled person could clearly attribute a disease or group of diseases to this functional definition.
5. In the board's view, the skilled person reading this definition in claim 3 would be struck, on the one hand, by the explicit mention and the specific definition of

- the first population of cells and by the explicit mention, but absence of specific definition of the second population of cells, on the other hand.
6. Had the disease in claim 3 be defined simply as, for example, the "induction of apoptosis in tumour cells" the skilled person would certainly, in particular in the context of the present application (see point 22.1 below), have implicitly complemented this explicit definition by considering that the type of cells which should not be affected by apoptosis are non-tumour cells and would thus have interpreted claim 3 as relating to the treatment of cancer. However, the explicit, but unspecified reference to a second population of cells in claim 3 raises uncertainty about which cells, in addition to non-tumour cells, are concerned and thus which diseases in addition to cancer are defined by the expression at issue.
 7. Hence, the board concludes that claim 3 does not clearly and unambiguously define the disease or disorder to be treated with rimcazole. Therefore, the main request is refused because claim 3 does not fulfil the requirements of Article 84 EPC.

Auxiliary requests 1 to 2

Article 84 EPC

8. Claim 13 relates to a kit comprising, inter alia, "directions instructing administration of the composition in a manner which would result in the preferential induction of apoptosis in a first population of cells compared to a second population of cells, wherein the cells of the first population are

tumour cells and the cells of the second population are non-tumour cells".

9. In view of the explicit indication in claim 13 of the induction of apoptosis in tumour cells, but not in non-tumour cells, the skilled person would prima facie, and in particular in the context of the present application (see below point 22.1), perceive that claim 13 relates to a kit for the treatment of cancer (see also point 22.1 below).
10. Claim 14 is dependent on claim 13 and is directed to "[t]he kit of claim 13 wherein the kit is for the treatment of cancer."
11. Thus, prima facie and when regarded separately, the meaning of both claims 13 and 14 is clear, i.e. they both relate to the same subject-matter.
12. However, as noted in point 2 above, the meaning of a claims is determined in the context of the whole application, i.e. also in context with other claims.
 - 12.1 When claim 13 is regarded in context with claim 14 an uncertainty about the meaning of claim 13 arises in because claim 14 is dependent on claim 13, yet covers the same subject-matter. Thus, since it is therefore not clear which subject-matter is defined by claim 13, an objection of lack of clarity arises.
13. All the above observations apply equally to auxiliary request 2 in which claims 13 and 14 are identical with claims 13 and 14 of auxiliary request 1.

14. Hence, auxiliary requests 1 and 2 are rejected because they do not fulfil the requirements of Article 84 EPC.

Auxiliary request 3

Correction of an obvious error

15. The request for the correction of an obvious error in claim 4 was filed at a very late point in time during the appeal proceedings, i.e. during the oral proceedings. However, since the request simply concerned the deletion of the word "rimcazole" in claim 4, the board could easily deal with the request, although it was presented late. In fact, the board had expected such a request (see section XIV). Therefore, the request is admitted.
16. Rule 139 EPC (Rule 88 EPC 1973) stipulates that if a request for correction "concerns the description, claims or drawings, the correction must be obvious in the sense that it is immediately evident that nothing else would have been intended than what is offered as the correction.".
17. The appellant requests the deletion of the reference to rimcazole in claim 4. Claim 4, which is dependent on claim 1, relates to the use of a medicament which medicament comprises in addition to a first a second sigma receptor ligand. In the board's view, there is no doubt that claim 4 defines a medicament comprising two different sigma receptor ligands. Since, in view of present claim 1, rimcazole is a mandatory constituent of the anti-cancer medicament, rimcazole cannot be considered as a "second" receptor ligand in the context of claim 4.

18. Hence, it is obvious that the word "rimcazole" should be absent from claim 4. As already mentioned in its communication, the board considers that this word was not deleted by oversight when claim 1 was restricted to the use of rimcazole.

19. Thus, the request for correction is allowed pursuant to Rule 139 EPC. The correction has been carried out by the board during the oral proceedings.

Article 123(2) EPC

20. Pursuant to Article 123(2) EPC the European patent application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. According to established case law the content of an application is the explicit or implicit information that the skilled person, reading the application with his/her background knowledge, would clearly and unambiguously derive from it.

21. Claim 1 relates to the use of rimcazole for the preparation of a medicament for the treatment of cancer.

22. There is no explicit basis for this subject-matter in the application as filed. There is however an implicit disclosure as follows:

22.1 It is stated in the first paragraph of the application as filed that the invention "relates to materials and methods relating to the **induction** of cell division cycle arrest and/or **apoptosis** in target cells. In

particular **the target cells may be tumour cells** or cells involved in inflammatory disease processes." (emphasis added). In the board's view, the skilled person would normally understand the expression "tumour cells" as referring to cells of a tumour of malignant cells and would consequently understand that the disease alluded to by the expression "the target cells may be tumour cells" is cancer.

22.2 According to the application as filed the activation of the cell death programme, i.e. of apoptosis - which is the mechanism relied on for the treatment of cancer in the context of the present application - is achieved in different ways. One of them is the administration of a ligand for a sigma receptor. It is stated on page 29, lines 10 to 16 that "[a]ccording to another aspect of the present invention there is provided a composition for the preferential induction of cell division cycle arrest and/or apoptosis in a first population of cells compared to a second population of cells, which composition comprises **a ligand for a sigma receptor**. "Sigma receptor ligands" are defined and explained above. The cells are stated as above and may be tumour cells" (emphasis added). Similarly, claim 19 as filed relates to "[a] composition for the preferential induction of cell division cycle arrest and/or apoptosis in a first population of cells compared to a second population of cells, which composition comprises a ligand for a sigma receptor."

22.3 The use of the composition as recited above is derivable from page 29, lines 22 to 27 disclosing that [t]he present invention also provides a method for the preferential induction of cell division cycle arrest

and/or apoptosis, in a first population of cells compared to a second population of cells which comprises exposing cells to a ligand for a sigma receptor. **The method may be employed to treat a patient ...**" (emphasis added) . On page 30, lines 5 to 14 it is stated that the composition may come with instructions directing "administration of the composition to a patient with or at risk of a tumour".

22.4 A list of sigma receptor ligands is disclosed on page 19, lines 24 to 26 including inter alia rimcazole.

Example 10 investigates the potential of rimcazole, haloperidol and cis-U50488 to inhibit the growth of MDA MB 468 carcinoma xenografts in mice. Rimcazole is highlighted as particularly effective in inhibiting tumour growth (page 59, line 34 to page 60, line 2).

22.5 In summary, the basis in the application as filed for claim 1 is in particular found on pages 19, 29 and 30, example 10 and claim 19 as filed.

23. Claim 2 is based on claim 33 as filed as far as the treatment of Hodgkins lymphoma is concerned. Figure 10a shows apoptosis of lung carcinoma cells in response to rimcazole (see column entitled "Rimcazole (0.1 mM)) and is therefore basis for the lung cancer-aspect of claim 2 (see also the description of the figure on page 34, lines 17 to 20). Figure 12 shows the activity of rimcazole on breast carcinoma cells and late-stage breast carcinoma cells and thus provides basis for the embodiment of claim 2 relating to breast cancer.

24. Claim 3 is based on page 30, lines 15 to 20 or claim 24 as filed in combination with page 19, lines 20 to 23 specifying the kappa receptor agonists mentioned in the claim.
25. The use of rimcazole in combination with a second sigma receptor ligand according to claim 4 is derivable from claim 35 as filed in combination with page 19, line 24 to page 20, line 12.
26. A combination of rimcazole with cis-U50488 for cancer treatment as claimed in claim 5 is for example disclosed on page 15, lines 22 to 25.
27. Claim 6, i.e. the use of a medicament that in addition to rimcazole comprises an NFκB activating agent, is disclosed on page 39, lines 13 to 16 stating that "[t]he cooperation of TNF [note by the board: according to page 22, TNF is an NFκB activating agent] is seen with all opioid-like compounds which induce apoptosis: these include naltrindole, trans-U50488, noscapine and sigma receptor ligands including haloperidol and rimcazole."
28. Claim 7 is based on claims 36 and 37 as filed.
29. Thus, the requirements of Article 123(2) EPC are fulfilled.

Article 84 EPC

30. The board has no objections.
31. In particular, the board considers claim 6, which contains a reference to "Table 1" to be in accordance with Article 84 EPC in connection with Rule 43(6) EPC for the following reasons.
- 31.1 The board notes that there is no table entitled "Table 1" in the application. However, firstly, there is only one part of the application which clearly is in tabular form, i.e. pages 22 to 24. Secondly, the paragraph before the start of the table on pages 22 to 24 deals with NFκB activating agents and ends by stating "[f]urther exemplary agents are named in the following table." Thus, it is clear that the reference to "Table 1" in claim 6 refers to pages 22 to 24 of the description.
32. Rule 43(6) EPC stipulates that "[e]xcept where absolutely necessary, claims shall not rely on references to the description or drawings in specifying the technical features of the invention".
33. The table on pages 22 to 24 lists in toto 70 compounds (for example, TNF), groups of compounds (for example, lectins), microorganisms (for example, Mycobacterium tuberculosis), viruses (for example, Epstein-Barr virus) and conditions (for example, UV light) that activate NFκB. Although this list could have been incorporated into claim 6, the board considers that the conciseness and readability of the claim would suffer from such a complete recitation. Therefore, the present case

represents an allowable exception in accordance with Rule 43(6) EPC.

34. The requirements of Article 84 EPC are fulfilled.

Article 83 EPC

35. Article 83 EPC requires that the European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In relation to claims to a second medical use, this means that for acknowledging that the requirements of Article 83 EPC are fulfilled, it is not only necessary that the skilled person is enabled to make or obtain the compounds to be used on the basis of the disclosure in the application and/or his or her common general knowledge, but also, that there is, e.g. evidence in the application that the therapeutic effect is achieved (for example T 609/02, point 9 of the reasons.)

36. Rimcazole and all the other compounds referred to in the claims are known.

37. The potential medical use of rimcazole for cancer treatment is demonstrated by Example 10 and Figure 15 disclosing that rimcazole significantly inhibits the growth of tumour explants in mice without deleterious side effects.

38. For completeness it is noted that the board considers that the results disclosed in post-published document D15 support the potential usefulness of rimcazole as an anti-cancer agent. They show that rimcazole has

preferential cell killing activity in tumour cells compared to normal cells.

39. The requirements of Article 83 EPC are fulfilled.

Article 54 EPC

40. Document D3, which the examining division in the decision under appeal found to anticipate the subject-matter of claims 1 to 7 and 14 to 18 of the main request then on file, discloses the use of a cytotoxic substance such as anthracycline in combination with an inhibitor of a protein mediating the multidrug resistance, such as an alkaloid for the treatment of cancer (see for example the abstract). Thus, the combination of features of present claim 1 are not disclosed in document D3.

41. The board has moreover assessed the relevance of document D1 which is a patent application, cited also in the present application, naming the same applicant as the present application and relating also to the induction of apoptosis for the treatment of, inter alia, cancer (see for example page 10, lines 11 to 19 in combination with page 11, lines 30 to 31 of document D1).

41.1 The agents for inducing apoptosis according to document D1 are, inter alia, "an agent which acts as an antagonist at receptor(s) related or identical to the delta opioid receptor, or an agent which acts as an agonist at receptor(s) related or identical to the kappa opioid receptor" (see page 10, lines 17 to 19).

41.2 As far as the meaning of the word "related" with respect to delta or kappa opioid receptors in the passage cited above is concerned, the following is disclosed on page 2, line 24 to page 3, line 1 of document D1 (literature references omitted by the board): "Opioid receptor subtypes based on differences in the binding profiles of natural and synthetic ligands have also been suggested, including mu1 and mu2 and kappa1 and kappa2. Tentative assignments of receptor subtypes to those cloned so far include kappa1 and mu2. Delta opioid receptors independently cloned from the same cell line, found to have a sequence difference in one region, may represent different delta receptor subtypes which co-exist in the same cell. Based on pharmacological data, further subdivisions of receptor subtypes, **and additional main receptor types including sigma**, epsilon and zeta have also been proposed." (emphasis added).

41.3 Thus, document D1 mentions sigma receptors, but teaches that they are a "main receptor type". In the board's view, the document therefore does not disclose that sigma receptors are "related" to kappa or delta receptors.

41.4 Therefore, document D1 cannot be considered as disclosing generally that agents binding to sigma receptors are useful for inducing apoptosis in the context of cancer treatment. Moreover, it does not mention specifically a single sigma receptor ligand, let alone rimcazole. Hence the subject-matter of claim 1 is not disclosed in document D1.

42. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC

Closest prior art; problem and solution

43. When taking into account well-established case law stipulating that the primary criterion for determining the closest prior art document for assessing inventive step is that it discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention, the board considers that any of the known cancer treatments, for example administration of ionising radiation or daunorubicin, as mentioned on page 6, lines 28 to 31 of the application, may be regarded as the closest prior art in relation to the presently claimed subject-matter.
44. Consequently, the problem to be solved is considered as the provision of an alternative treatment for cancer.
45. The solution according to the present claims is the use of the compound rimcazole.
46. For the reasons given above in points 37 and 38, the board is satisfied that the above-formulated problem is solved.

Obviousness

47. Given that "absolute proof" for the achievement of a therapeutic effect is not required according to the case law (see for example decision T 903/05, point 19, last paragraph of the reasons; decision T 391/07, point 20 of the reasons; decision T 394/06, point 13 of the reasons in combination with page 6, last paragraph to

page 8, first paragraph of "Facts and Submissions" in relation to inventive step and decision T 609/02 in relation to sufficiency of disclosure), the question in the present case is whether or not the skilled person would consider the compound rimcazole as a potential candidate for cancer treatment.

Documents D2 and D5

48. In the decision under appeal the examining division reasoned that the then-claimed subject-matter was obvious in view of documents D2 and D5. The board considers that these two documents are also the most relevant ones among those available in these proceedings for assessing the inventive step of the subject-matter under consideration now.
49. Document D5 discloses the existence of sigma receptor subtypes in different human and rodent tumour cell lines. Sigma receptor ligands other than rimcazole are used in the assays. However, in the discussion section on page 412, second column it is stated in general terms: "These results suggest that sigma receptors play some important role in the maintenance of cellular viability and the possible utility of sigma ligands as antitumor agents."
50. Document D2 discloses studies in which the ability of several sigma receptor ligands, among them rimcazole, to inhibit cell proliferation in mammary and colon carcinoma cell lines and melanoma cells in culture is tested. It was found that 25 to 100 μM of rimcazole produced 37% to 97% inhibition of MCF-7 colon cell and

inhibition of 24% to 98% of melanoma cell growth (Table 1 of document D2).

51. The appellant argues that even if the disclosure of growth inhibition of cells derived from tumours by rimcazole was considered as a suggestion to use rimcazole for the treatment of cancer, the claimed subject-matter was not obvious in view of either document D2 alone or in combination with document D5 for the following reason which was submitted for the first time during the appeal proceedings.
52. According to Table 1 of document D2 the concentration of rimcazole required in cell culture to induce cell death is at least 25 μM .
53. Rimcazole was originally developed as an anti-psychotic drug. Document D13 describes the results of an early phase II clinical trial of rimcazole (termed therein BW234U) in the treatment of acute schizophrenia. It shows that administration of rimcazole to humans at a dose of 125 mg/day results in a plasma concentration of the drug of 56.9 ng/ml (see page 283, first column, first full paragraph and second column, third full paragraph). This corresponds to a concentration of 0.18 μM (the molecular mass of rimcazole being 321.5 g/mole). Document D13 also discloses that plasma levels of rimcazole correlate with the dose (see page 283, second column, third full paragraph).
54. Thus, to achieve in a human patient a plasma concentration of 25 μM as required for cell death according to the cell culture assay in document D2, an oral dose of 17.4 g would be needed. Furthermore, for

achieving a dose at which more than 90% of the tumour cells are killed - a level which would be expected by the skilled person to be necessary for cancer treatment - a plasma concentration of 50 μM would be required according to document D2. This would equate to a daily dose of even 34.8 g.

55. Document D13 discloses that doses such as 0.5 g/day of rimcazole produce unacceptable side effects in humans, such as tremors, muscle fasciculations, EEG abnormalities and grand-mal seizures (see page 284, under "Discussion").
56. However, the application of a dose necessary for cancer treatment in humans as extrapolated from document D2 - 34.8 g - would be far beyond the dose found in document D13 to produce the unacceptable side effects. Moreover, such a high dose would be far too large to be administered on a daily basis and reconcilable with patient compliance.
57. Thus, in view of the disclosure in document D13, the skilled person would not have considered using the specific sigma receptor ligand rimcazole in the treatment of cancer in the light of the teaching in document D2. This attitude would not have been changed by the general statement in document D5.
58. The boards find this argumentation persuasive.

It is thus concluded that the skilled person would neither have pursued rimcazole as a medicament for cancer treatment in the light of document D2 alone nor in combination with document D5.

Document D1

59. The board has furthermore assessed the relevance of document D1 for the inventiveness of the claimed subject-matter. As observed above, document D1 teaches to use ligands of delta and kappa opioid receptors for the treatment of cancer. However, neither this document alone nor in combination with any other of the documents on file suggests that ligands of sigma receptors could be used as equivalents to the delta and kappa receptors for a use according to document D1 and hence, the skilled person would not be motivated by this document alone or in combination to use a sigma receptor ligand, let alone rimcazole, for the treatment of cancer. For this reason the claimed subject-matter is not considered as obvious in the light of document D1 alone or in combination.
60. Thus, the subject-matter of claim 1 and of dependent claims 2 to 7 involves an inventive step. The requirements of Article 56 EPC are fulfilled.

Remittal

61. The board received the proposal for an adapted description only very shortly before the oral proceedings. According to the appellant it should contain pages 1 to 17, 20 to 24 and 31 to 63 of the application as filed and amended pages 18, 19 and 25 to 30.
62. The board considers that, prima facie, the proposed amendments appear to be insufficient to properly adapt

the description to the subject-matter to which the claims are limited. For example, according to the description as filed the invention consists of two separate ways of inducing apoptosis for the treatment of cancer or inflammatory diseases, (i) the administration of a combination of an opioid or an opioid-like receptor ligand in combination with an NFκB activating agent (page 25, line 29 to page 26, line 1) or (ii) the administration of a sigma receptor ligand (page 29, lines 10 to 15). The claims are restricted to one embodiment of the second aspect, i.e. the use of the rimcazole for the treatment of cancer. However, for example, Example 1.1, which appears to relate to the first aspect of the invention, has not been deleted.

63. Since, given its absence, the appellant's representative could not be heard with regard to objections regarding the insufficient adaptation of the description at the oral proceedings, the board considered it appropriate - as already announced in its communication (see section XIV above) - to remit the case to the first instance for the adaptation of the description.

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 with the order to grant a patent on the basis of claims 1 to 7 of auxiliary request 3 filed on 6 October and corrected on 11 October 2010 and a description and figures to be adapted.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith