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Datasheet for the decision of 31 January 2013

Case Number: T 2245/10 - 3.3.02

Application Number: 00932669.5

Publication Number: 1178786

IPC: A61K 31/00, A61K 47/42

Language of the proceedings: EN

Title of invention:
Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof

Applicant:
Abraxis BioScience, LLC

Headword:
Protein stabilized pharmacologically active agents/ABRAXIS BIOSCIENCE, LLC

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - (no): definition of a technical problem which is in contradiction to the original teaching is not allowable"

Decisions cited:
T 0155/85, T 0115/89

Catchword:
-

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Case Number: T 2245/10 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 31 January 2013

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 7 June 2010 refusing European patent application No. 00932669.5 pursuant to Article 97(2) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent application No. 00 932 669.5 was refused by a decision of the examining division pronounced on 30 November 2009 and dispatched on 7 June 2010 on the basis of Article 97(2) EPC on the grounds that main request and auxiliary requests I and II lacked inventive step.

II. The documents cited during the examination and appeal proceedings included the following:

(3) WO 99/00113 (corrected version)
(4) WO 98/24427
(5) S.S. Legha, et al., Cancer, (1990) 65, 2478-2481
(6) A.I. Einzig, et al., Investigational New Drugs (1991) 9, 59-64
(9) S. Aamdal, et al., Eur. J. Cancer, (1994) 30A(8), 1061-1064
(10) A.Y. Bedikian, et al., Journal of Clinical Oncology, (1995) 13(12), 2895-2899
(11) E. Hersh, et al., "Phase II trial of ABI-007 (Abraxane) in previously treated and chemotherapy naive patients with metastatic melanoma (2006)
(14) E. Hersh, et al., "Phase 3 study of nab-Paclitaxel vs Dacarbazine in Chemotherapy-naïve Patients with Metastatic Malignant Melanoma", presented at: The Society of Melanoma Research; November 8-11, 2012, Los Angeles, CA
(15) R.L. Comis, Cancer Treatment Reports, (1976) 60, 165-176.

III. Regarding inventive step, the examining division essentially argued as follows: starting from document (3) as closest prior art, the provision of further medical uses for protein coated taxane compositions, characterised by less severe side effects and higher efficacy, was defined as the problem to be solved. The solution in the form of the subject-matter claimed in claim 1 of the main request was rendered obvious by combining the teaching of document (3) with the teaching of any of documents (4), (5), (6), (9) or (10). The data provided in example 27 of the application as filed in connection with the efficacy of paclitaxel in the treatment of malignant tumours were not surprising in the light of the prior art and could therefore not establish an inventive step. This reasoning applied *mutatis mutandis* to auxiliary requests I and II.

IV. The appellant (applicant) lodged an appeal against this decision. With the statement of the grounds of appeal, the appellant submitted a new main request and auxiliary requests I and II. The independent claims read as follows:

(i) Main request

"1. A composition comprising a taxane in the form of particles coated with protein for use in the treatment of a disease selected from melanoma, psoriasis, multiple sclerosis, and renal cell carcinoma, wherein the average diameter of said particles is less than about 1 micron."

(ii) Auxiliary request I

"1. A composition comprising a taxane in the form of particles coated with protein for use in the treatment of a disease selected from melanoma and psoriasis, wherein the average diameter of said particles is less than about 1 micron."

Auxiliary request II

"1. A composition comprising a taxane in the form of particles coated with protein for use in the treatment of melanoma, wherein the average diameter of said particles is less than about 1 micron."

V. Regarding inventive step in connection with the treatment of melanoma, the appellant essentially argued as follows:

The present invention concerned the treatment of malignant melanoma. As dacarbazine (DTIC) had been considered to be the "gold standard" for treating melanoma prior to the effective filing date of the present application, a document such as document (15) which disclosed successful treatment of melanoma with DTIC constituted the closest prior art. In view of the studies made in documents (11) and (14), in which the product defined in the present claims compared very favourably to DTIC in the treatment of malignant melanoma, an inventive step had to be acknowledged. Alternatively, document (5) could be defined as closest prior art. Again, there were various reasons for an inventive step: firstly, the coated taxane particles of the present invention constituted a completely

different drug as compared to the taxanes according to document (5). This was due to the fact that, in contrast to document (5) where the taxane was stabilised by a Cremaphore, the taxane according to the present invention was protein coated and thus did not require the presence of further stabilising agents, which was beneficial, as Cremaphores were known for unwanted side effects. Secondly, it was stated in document (5) (see the first paragraph of the section "Discussion" on page 2480) that Taxol had a low response rate despite a very favourable patient population used for the study conducted therein, which dissuaded the skilled person from further research in that direction. On the other hand, document (3), which had been selected as closest prior art in the decision under appeal and which disclosed coated taxane particles as used in the present invention, was completely silent as to treatment of malignant melanoma. The skilled person would therefore not combine the teachings of these documents as there was no reasonable expectation of success for such a combination. Apart from the reduction of unwanted side effects due to the absence of Cremaphores mentioned above, the beneficial effects obtainable by using coated taxane particles for treating melanoma included surprisingly high response rates and medium progression free survival times for both pretreated and CN patients (chemotherapy naive patients). Reference was made to example 27 of the present application. The appellant mentioned as a further indication for an inventive step the fact that the high response rates and long progression free survival times had been obtained with similar drug concentrations as compared to the prior art, which meant that the reasoning of the examining

division, according to which the foreseeable lower level of unwanted side effects allowed higher taxane concentrations and therefore an improved antitumour activity, was wrong.

VI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, on the basis of the first or second auxiliary request, filed with the statement of grounds of appeal dated 12 October 2010.

Reasons for the decision

1. The appeal is admissible.

2. Main request - inventive step

2.1 Object of the invention

The present invention concerns the provision of a composition for administering a taxane to patients suffering from a proliferative disease, in particular malignant melanoma, wherein the toxicity of the taxane should be reduced (see page 14, lines 1 to 6 and page 36, line 4 to page 37, line 3).

2.2 Closest prior art

2.2.1 At the oral proceedings before the board, the appellant initially defined document (15), which discloses the use of DTIC for treating malignant melanoma, as closest prior art. In contrast thereto, the examining division started from document (3), which discloses the use of

protein coated taxane particles such as Capxol^{R} (protein coated paclitaxel), which are identical to the particles according to the present invention, for the treatment of diseases such as prostate cancer, orchidectomy, pancreatic cancer and brain tumour (see page 22, lines 10 to 15; page 28, lines 14-18; claims 1 and 7).

2.2.2 The board, however, notes that in the present case a document should be selected as closest prior art which discloses the use of a taxane for the treatment of malignant melanoma. As a consequence, document (5) constitutes the closest prior art.

Document (5) concerns a study in which 25 patients with metastatic melanoma who were previously untreated received Taxol, which contains paclitaxel as active agent (see page 1, line 13 of the application) at a starting dose of 250 mg/m^2 delivered as a continuous intravenous infusion over 24 hours, at 3-week intervals (see abstract). In contrast to the protein coated taxane particles of the present invention, Taxol according to document (5) was a conventional formulation in which the active agent was stabilised by Cremaphore. As was correctly pointed out by the appellant (see point V above), the results did not live up to the high expectations of the physicians carrying out this study because of a response rate of below 20% despite a very favourable patient population (see the first paragraph of the section "Discussion" on page 2480). The authors of document (5) did, however, not conclude therefrom that treatment of such melanoma with Taxol should be discontinued. On the contrary: taking into account the "paucity of other drugs with similar

or better activity against melanoma…" (see penultimate paragraph of the right-hand column on page 2480), it was recommended to use a Taxol dose of 200 mg/m^2 as a single agent for the treatment of patients with metastatic melanoma (see paragraph bridging pages 2480 and 2481). This statement was followed by the conclusions that "Taxol is an interesting drug which, besides showing activity against melanoma, has also shown activity against refractory carcinoma of the ovary" and that "…there is considerable potential for Taxol to be a drug with good future". As a consequence, document (5) qualifies as closest prior art.

2.3 Problem to be solved

2.3.1 When formulating the problem to be solved with regard to document (5), it has to be evaluated what further effects, if any, are achieved by the selection of protein coated taxane in addition to the reduced toxicity. One direct consequence of the reduced toxicity consists in the possibility to administer higher taxane doses. According to the passage on page 37, lines 17 to 20 of the application, the dose administered is "typically larger than doses administered as part of conventional formulation". This teaching is confirmed by example 27 which concerns a phase I clinical study in which 17 patients suffering from metastatic malignant melanoma are treated with Capxol^R. In this study the maximum single dose administered was 375 mg/m^2, which is much higher than the approved dose of 175 mg/m^2 for paclitaxel, when administered as Taxol (see page 63, lines 3 to 6 of the application), and higher than the dose of 250 mg/m^2, administered in the study according to document (5).

However, this aspect cannot be taken into consideration for the definition of the problem to be solved, as claim 1 of the main request does not define the concentration of the taxane to be administered to the patient. As a consequence, the problem to be solved would have to be defined as provision of a taxane composition for treating melanoma, which is characterised by less unwanted side effects.

2.3.2 The appellant, making reference to post-published document (11) alleged an increased drug efficacy as a further effect that had to be taken into consideration for the assessment of inventive step. In document (11) previously treated patients and CN patients were treated with 100 mg/m^2 and 150 mg/m^2 Abraxane (= protein coated paclitaxel corresponding to Capxol^R), yielding an overall response of 38% for pretreated patients of 49% for CN patients. This was much higher than the response rates in document (5), which had been achieved with 250 mg/m^2 of Taxol. It could not be predicted that the same or even lower doses of taxanes would lead to such a significant increase in efficacy of the therapy, in particular with regard to the previously treated patients, who usually showed limited response. Similar results were shown in documents (9) and (10) for docetaxel as active agent. As a consequence, the problem to be solved with regard to document (5) concerned the provision of a less toxic and more efficient taxane composition for treating melanoma.

2.3.3 In this context, the question arises whether this aspect is encompassed by the technical teaching of the original application, which in a primary aspect is concerned with methods for the *in vivo* delivery of

substantially water insoluble pharmacologically active agents in general as well as the provision of dispersible colloidal systems containing water insoluble pharmacologically active agents (see page 1, lines 11 to 15). The treatment of melanoma is a marginal point of the broad and general teaching of the original application and is first mentioned on page 36, where the treatment of proliferative diseases such as psoriasis, multiple sclerosis, vascular restinosis (see page 36, lines 15 to 16) or cancers such as malignant melanoma (see page 37, line 2) can be treated with suitable pharmacologically active agents including taxanes such as paclitaxel or docetaxel (see page 36, lines 20 to 22). It is important to note that this passage also contains the information that the protein coated particles of the present invention reduce myelosuppression and neurotoxicity (see page 35, line 27 to page 36, line 6), so that the dose of suitable pharmacologically active agent administered to the patient is "typically larger than doses administered as part of conventional formulations" (see page 37, lines 17-19), which means that this aspect of the original teaching, i.e. treatment of melanoma by administration of protein coated taxane, is linked to the administration of higher than the usual doses.

This teaching is put into practice in example 27, which is the only example relevant for the treatment of melanoma by administering protein coated taxane. The board notes in this context that examples 28 and 29, though also mentioning treatment of melanoma, are not relevant for the following reasons: example 28 primarily concerns intra-arterial administration of Capxol^{R} for the treatment of liver tumours and/or solid

tumours with local-regional involvement (see page 65, lines 4 to 7). Although the long list of patients suffering from various types of cancers includes patients suffering from melanoma (see page 65, lines 16 to 20), these patients do not figure in the list of patients for which a response to the treatment had been observed (see page 65, lines 20 to 22). As a consequence, example 28 is not relevant for the subject-matter claimed in the main request. Example 29 is not relevant, as it relates to a combination therapy of Capxol^{R} with IL-2.

Example 27 concerns a phase I clinical study in which 17 patients exhibiting advanced matastases were treated with Capxol^{R} (containing the taxane paclitaxel). Six patients were suffering from malignant melanoma, the remaining 11 subjects from breast cancer. Starting from an initial dose level of 135 mg/m^2, the subsequent doses were increased to the next higher paclitaxel single dose level if there were no significant adverse effects in the subject. The maximum single dose administered in this study was 375 mg/m^2, for which no significant adverse effects were noted. Administration of paclitaxel as protein coated particle at single dose levels as high as from 500 mg/m^2 or 2000 mg/m^2 and beyond are contemplated in example 1.

2.3.4 To summarise:
the teaching of the original application, which is put into practice in example 27, tells the skilled person to use as high as possible doses of protein coated taxane for the treatment of melanoma. These doses are higher than the doses used for the administration of taxane in conventional galenic forms.

2.3.5 The board notes that redefinition of the problem to be solved is usually permissible, it is even necessary in cases in which prior art is found which is closer to the claimed invention than the prior art cited in the application as filed. Usually, it is also possible to base such a newly defined problem on post-published evidence provided that it is linked to and in line with the original technical teaching. Such a redefinition is, however, not acceptable in cases where the teaching of post-published evidence is used for defining a new technical problem which is in contradiction to the original teaching of the application as filed (T 155/85, point 12 of the Reasons and T 115/89, fourth paragraph of point 4 of the Reasons). This being the case in view of the fact that the original teaching does not foresee the use of conventional taxane doses for the treatment of melanoma, the problem to be solved concerns, as previously indicated, the provision of a taxane composition for treating melanoma, which is characterised by less unwanted side effects.

2.4 Solution

The proposed solution to this problem consists in the provision of protein coated taxane. Despite the fact that the patient group in example 27 of the present application is a mixed group in which only six out of 17 patients suffer from melanoma, the board is convinced that the results described therein are sufficient for demonstrating that this problem has been plausibly solved.

2.5 Obviousness

Document (3) discloses protein coated taxane particles which are identical to the particles of the present invention. This fact was not contested by the appellant. In fact in both document (3) and the present application, Capxol^{R}, a protein coated paclitaxel formulation, is used as preferred embodiment (see page 2, lines 6 to 9 of document (3) and example 27 of the present application). Document (3) repeatedly mentions that protein coated paclitaxel is characterised by a reduced degree of unwanted side effects, in particular as far as toxicity and myelosupression is concerned, as compared to uncoated formulations (see page 2, lines 6 to 9; page 28, lines 14 to 18; page 29, lines 13 to 19; page 31, lines 22 to 30; page 32, lines 11 to 17; page 33, lines 6 to 9; page 45, lines 24 to 27). As a consequence, the skilled person would replace the product of document (5) by Capxol^{R} in order to solve the problem defined above. Document (3) discloses on page 5, lines 22 to 25 that paclitaxel "has shown excellent antitumor activity in a wide variety of tumor models such as the B16 melanoma, L1210 leukemias, MX-1 mammary tumors, and CS1 colon tumor xenograft". The skilled person has therefore a strong motivation for combining the teachings of documents (3) and (5). As a consequence, the appellant's argument, according to which the fact that treatment of melanoma is not claimed in document (3) would keep the skilled person from such a combination, cannot be followed. As a consequence, the subject-matter of claim 1 of the main request does not meet the requirements of Article 56 EPC.

2.6 Further considerations

Document (3) also discloses the increased efficacy of Capxol^{R} as compared to conventional formulations. According to the passage on page 31, lines 16 to 20, it is "also very surprising that paclitaxel, when administered as Capxol^{TM}, is metabolized into its metabolites at a much slower rate than when administered as Taxol$^{®}$. **This represents increased anticancer activity for longer periods with similar doses of paclitaxel"** [emphasis by the board]. As a consequence, even if this aspect had been taken into consideration and the problem to be solved had been defined as proposed by the appellant (see point 2.3.2 above), the combination of documents (5) and (3) would still render the subject of claim 1 of the main request obvious.

2.7 In view of this finding, an evaluation of the further diseases to be treated by the protein coated taxane composition according to claim 1 of the main request is not necessary.

3. Auxiliary request I

Claim 1 of auxiliary request I is identical to claim 1 of the main request, except that the diseases to be treated are restricted to melanoma and psoriasis. As a consequence, the reasoning of point 2 above applies *mutatis mutandis* to claim 1 of auxiliary request I. The requirements of Article 56 EPC are therefore not met.

4. Auxiliary request II

Claim 1 of auxiliary request II is identical to claim 1 of the main request, except that melanoma is the only remaining disease to be treated. As a consequence, the reasoning of point 2 above applies *mutatis mutandis* to claim 1 of auxiliary request II. The requirements of Article 56 EPC are therefore not met.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman

N. Maslin U. Oswald