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Application No. / Patent No.	Ref.	Date
01 948 214.0 - 1216 / 1313508 /	X14173 EP	27.12.2010
Proprietor ELI LILLY AND COMPANY		

Decision rejecting the opposition (Art. 101(2) EPC)

The Opposition Division - at the oral proceedings dated 18.11.2010 - has decided:

The opposition(s) against the European patent EP-B- 1313508 is/are rejected.
The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Registered letter with advice of delivery
EPO Form 2330 12.07TRI

Opposition Division:

Chairman:	Bonzano, Camilla
2nd Examiner:	Bazzanini, Rita
1st Examiner:	Hoff, Philippe

Bolten, Eleonore
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Enclosure(s): 17 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97 - 98 EPC (Form 2019)
Minutes of oral proceedings

to EPO postal service: 21.12.10

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EPO Form 2330 12.07TRI

1 SUMMARY OF FACTS AND SUBMISSIONS

1.1 European patent EP-B1-1 313 508 is based upon European patent application number 01948214.0. Date of filing: 15.06.2001. Claimed priorities: 30.06.2000 US 215310P; 27.09.2000 US 235859P and 18.04.2001 US 284448P.

The mention of the grant of the patent has been published in the European Patent Bulletin 2007/16.

Proprietor of the patent (P): Eli Lilly, Indianapolis (US)

Opponent 1 (O1) : Teva Pharmaceutical Industries Ltd., Petah Tqva (IL)

1.2 The text of the claims under consideration is in the form as granted.

1.3 With the notice of opposition, filed on 17.01.2008, O1 requested the complete revocation of the patent under Article 102(1) EPC, on the grounds of Articles 100(a) and (b) because its subject-matter is not patentable (Article 53(c) EPC), not novel (Article 54 EPC), does not involve an inventive step (Article 56 EPC) and because the patent opposed does not disclose the invention sufficiently (Article 83 EPC).

Documents D1-D14 were cited

1.4 With his letter dated 09.04.2009, P submitted that the claims as granted meet the requirements of the EPC and thus requested rejection of the opposition under Article 102(2) EPC.

Documents D15 and D16 were cited

1.5 In response to the submission filed by P, O1 filed additional arguments and maintained each and every ground stated in the notice of opposition.

Documents D17-D25 were cited

1.6 All parties have made an auxiliary request for oral proceedings.

1.7 In a communication dated 29.04.2010, the opposition division (OD) summoned the parties to oral proceedings on18.11.2010. The preliminary opinion of the OD was, inter alia, that the claims as granted met the requirements of Articles 53(c), 83 and 54 EPC.

1.8 With a letter dated 15.10.2010, O1 filed further submissions with regard the isssue of inventive step and three new documents D26-D28.

1.9 With a letter dated 18.10.2010, P filed a first auxiliary request which introduces the features of claim 2 into claim 1 of the patent as granted.

A new document D29 was additionally filed with a letter dated 02.11.2010.

1.10 Oral proceedings took place the 18.11.2010. As for further details reference is made to the minutes of the oral proceedings. At the end of the oral proceedings, the Chairperson of the OD announced that the opposition is rejected and the European patent maintained as granted.

1.11 The following documents have been cited by the parties:

D1: Hazarika, M et al.: "FDA Drug Approval Summaries: Pemetrexed (Alimta)", The Oncologist (2004), 9: 482 - 488.

D2: Eli Lilly Summary ID#2258 - Clinical Study Summary: Study H3E - MC - JMCH.

D3: Vogelzang NJ et al.: "Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma." J. Clin. Oncol. (2003), 21(4): 2636 - 2644.

D4: Eli Lilly Summary ID#3653 - Clinical Study Summary: Study H3E - MC - JMDR.

D5: Scagliotti G V et al.: "Phase II study of pemetrexed with and without Folic Acid and Vitamin B12 as front - line therapy in malignant pleural mesothelioma", J. Clin. Oncol. (2004), 21(8): 1556 - 1561.

D6: Clinical Trials Dictionary from ClinicalTrials.gov web site.

D7: Official text of Section 312.21 of Title 21 of the Code of Federal Regulations (1997 edition).

D8(a) and **D8** (b): "Metabolism at a Glance", edited by Blackwell Science (1998 edition), pages 54 - 57.

D9: Niyikiza C et al.: "LY231 514 (MTA): relationship of vitamin metabolite profile to toxicity", American Society of Clinical Oncology (ASCO) Meeting Abstract No.2139 (1998).

D10: Hammond L et at.: "A phase I and pharmacokinetic (PK) study of the multitarget antifol (MTA) LY211514 with folic acid", American Society of Clinical Oncology (ASCO) Meeting Abstract No. 866 (1998).

D11: Morgan et al.: "Folic acid supplementation prevents deficient blood folate levels and hyperhomocysteinemia during long - term, low dose methotrexate therapy for rheumatoid arthritis: implications for cardiovascular disease prevention." J. Rheumatoh (1998), 25:441 - 446.

D12: Worzalla et al.: "Role of Folic acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231 514", Anticancer Research (1998), 18: 3235 -3240.

D13: "Clinical Chemistry: principle, procedures, correlation", third edition (1996), published by Lippincott: pages 61 8 - 627.

D14: U.K. Label for Alimta® (source: www.emc.medicines.org.UK).

D15: Redacted UK Agreement for clinical trial JMCH

D16: Redacteci UK Agreement for clinical trial JMDR

D17: Mutschler, E.: Arzneimittelwirkungen, 5th ed. (1986): 665.

D18: Estler, et al.: Pharmakologie und Toxikologie, 5th ed. (2000): 684.

D19: Barak, et al.: "Vitamin B12 as a Possible Adjunct in Prevention of Methotrexate Hepatotoxicity", Biochemical Archives (1985), vol. 1: 139 - 142.

D20: Arsenyan, et al.: "Influence of Methylcobalamin on the Antineoplastic Activity of Methotrexate", Pharmaceutical Chemistry Journal (1978), vol. 10: 1299 - 1304.

D21: Maysishecheva, N.y., et al.: "Antitumor Activity of Methotrexate When Used in Combination with Cobalamine Derivatives", Eksperimentalnaya Onkologija (1982), vol. 4, no. 5: 29 - 33.

D21A: Certified English translation of D21.

D22: Sofyina, Z.P., et al.: "Possibility of Potentiating the Antineoplastic Action of Folic Acid Antagonist by Methylcobalamine Analogs", Vestnik Akademli Medicinskich Nauk SSSR (1979), vol. 1: 72 - 78.

D22A: Certified English translation of D22.

D23: McDonald, A.C., et al.: "Clinical Phase I Study of LY231 514, a Multitargeted Antifolate, Administered by Daily x 5 q 21 Schedule", Annals of Oncology(1996), vol.

7: 85, Abstract No. 291.

D24: Fernandez, Dennis S., Huie James T.: “Strategic Balancing of Patent and FDA Approval Processes To Maximize Market Exclusivity”

D25: Davidson, Cliff: “Loss of Patent Rights - Experimental Use vs. On - Sale BarlPublic Use”

D26: Abstract No.907, Zervos et al.: "Functional folate status as a prognostic indicator of toxicity in clinical trials of the multitargeted antifolate LY231514", Proceedings of ASCO, Vol.16, 1997, page 256a

D27: Abstract No. 609P, Niyikiza et al.: "MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity", Annals of Oncology, Vol.9, Suppl. 4, 1998, page 126

D28: Calvert, Hilary: "An Overview of Folate Metabolism: Features Relevant to the Action of Toxicities of Antifolate Anticancer Agents", Seminars in Oncology, Vol.26, No.2, Suppl. 6 (1999), pages 3-10

D29: Savage D G et al.: "Sensitivity of Serum Methylmalonic Acid and Total Homocysteine Determinations for Diagnosing Cobalamin and Folate Deficiencies", Am J Med 96: 239-246, 1994

1.12 Claim 1 of the patent at issue relates to the use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof (said derivatives being further defined in claim 1).

REASONS FOR THE DECISION

1. Admissibility

The opposition is admissible because it meets the requirements of Articles 99(1) and 100 EPC and of Rule 76 EPC.

2. Second medical use claim (Article 100(a) in conjunction with Article 53(c) EPC)

2.1 O1 has argued that claim 1, which is drafted in the second medical use format, violates Article 53(c) EPC. According to O1, since the use of pemetrexed for inhibiting tumor growth was known at the priority date the purportedly new application in the claims is the combination therapy with vitamin B12. This falls in the realm of a dosage regime and consequently claim 1 should not be permitted in view of Article 53(c) EPC. Three decisions T317/95; T584/97 and T56/97 were cited in order to support O1's statement. The same holds true for its dependent claims 2-11.

2.2 In decision G5/83 the Enlarged Board of Appeal was concerned with a second (or further) medical use in situations were the first medical use was already known. The Enlarged Board of Appeal Stated : "*A European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application*".

2.3 The Opposition Division (OD) first notes that present claim 1 is in the approved format. A further medical use claim in the approved format must be treated as complying with Article 53(c) EPC (Article 52(4) EPC 1973) irrespective of the detail with which the therapy is specified (T1020/03).

In decision G5/83, it is clear that the Enlarged Board treats the uses that fall under Article 52(4) EPC in broad terms. This Board understands the use of the word "specified" to be merely by way of contrast to the unspecified therapy allowable in a claim for a first medical use and not as imposing any special conditions that a further medical use had to fulfil (T1020/03, point 7).This principle was confirmed by the decision G2/08 with respect to Article 54(5) EPC. The Enlarged Board of Appeal stated that "any" specific use not comprised in the state of the art may be eligible for patent protection under that Article and thus, the new use within the meaning of Article 54(5) EPC 2000 need not be the treatment of another disease (point 5.10.3).

2.4 In line with T1020/03 and G2/08, the OD considers that <u>every therapy</u> which falls within these broad terms that is not the first known therapy involving the composition, <u>including a combination therapy</u>, allows a claim in the approved form of making a preparation for this further use which claim will thereby avoid conflict with Article 53(c) EPC (Article 52(4) EPC 1973).

2.5 Furthermore, considering that present claim 1 can be regarded as of the dosage regimen type (as argued by O1), the principles elaborated by the Enlarged Board of Appeal in its decision G2/08 should apply in the present case. This means that where it is already known to use a medicament to treat an illness, Article 54(5) EPC does not exclude that this medicament be patented for use in a different treatment by therapy of the same illness. Such patenting is also not excluded where a dosage regime is the only feature claimed which is not comprised in the state of the art.

2.6 The OD is therefore of the opinion that the present claim 1 (and its dependent claims 2-11) is not excluded from patentability under Article 53(c) EPC 2000.

3 Insufficiency Disclosure (Article 100(b) in conjunction with Article 83 EPC)

3.1 O1 argued that the data of the opposed patent show that vitamin B12 alone cannot be used in patients undergoing pemetrexed treatment to effectively lower side effects. It is apparent from the results reported in patients that the improvement seen with vitamin B12 is rather minimal, whereas when folic acid is administered as well as the B12, the reduction in side effects is markedly improved. According to O1, the results in mice which show that addition of vitamin B12 to the diet of a subject receiving pemetrexed results in excellent antitumor activity with little or no toxic effects, are not representative for human. The reported results on human described on paragraph [0055] of the opposed patent would clearly show that vitamin B12 supplementation without folic acid has only a moderate effect on drug related toxicity and contradict the results on mice.

In this regard, O1 referred to D14 (the label for Alimta) which requires that both vitamin B12 and folic acid are to be given to patients prior to premetexed treatment.

With regard to the paragraph [0045] of the patent which refers to a pilot study in humans, O1 argued that no data/information were given about this study and therefore the alleged reduction of side effects with vitamin B12 alone is purely speculative.

O1 concluded that vitamin B12 alone cannot adequately reduce side effects as the opposed patent asserts. Consequently, claim 1 which does not necessarily require the presence of a folic acid is not sufficiently described.

Furthermore, O1 asserted that the opposed patent does not sufficiently enable the vitamin B12 derivatives mentioned in claim 1, nor are the folic protein binding agent other than folic acid sufficiently enabled by the data in the patent. All tests described in the patent are stated to have been carried out with vitamin B12 and folic acid. The decision T609/02 was cited to support his statement.

3.2 The OD is of the opinion that the present invention is sufficiently disclosed to be put into practice, in the sense that the skilled person knows which compounds to use and which disease to treat.

T609/02 appears not to apply, as this decision relates to the use of an unidentified chemical compound for the treatment of diseases which are merely functionally defined. Both the compound and the disease to be treated are clearly defined in the present case.

3.3 Furthermore, the OD does not share the point of view of O1 that the patent does not contain data supporting the use of pemetrexed and vitamin B12 alone.

The disclosure of the animal model test set out from page 5, paragraph [0034] to page 6, paragraph [0043] (patent) shows clearly that toxicity was reduced and that efficacy of pemetrexed against the implanted human MX-1 tumour was not diminished. Toxicity, in accordance with paragraphs [00037]- [0038] was measured through body weight with body weight loss indicating toxicity. Paragraph [0038] states that the animals treated with Alimta (100mg/kg) along with vitamin B12 gained weight whilst those treated with Alimta (150mg/kg) along with vitamin B12 maintained weight over the course of the experiment.

Human MX-1 breast carcinoma is a well known animal model for testing anticancer drugs. The OD is thus of the opinion that the reported activity of vitamin B12 on the toxicity of pemetrexed in this animal model makes plausible that vitamin B12 alone can adequately reduce toxicity in human.

This is confirmed by the studies in human described on paragraph [0055] which show that vitamin B12 supplementation with pemetrexed has a moderate effect on drug related toxicity, lowering drug related death from 4% to 3% (which is 25% of the total number of drug related deaths) and severe toxicities by about 25%. Even if the activity described is moderate, this effect is not negligible (reduction by 25%) which means that some patients clearly receive a therapeutic benefit from the supplementation.

Consequently, the OD does not share O1's point of view that vitamin B12 supplementation, without folic acid is devoid of any significant effect on the toxicity of premetrexed in view of the results of the clinical trials described on paragraph [0055] in the opposed patent.

The fact that the label of Alimta recommends the use of vitamin B12 and folic acid to reduce the incidence and severity of its side effects does not mean that vitamin B12 alone could not be useful in the prevention of said side effects.

The OD would like to note here that a positive effect of vitamin B12 supplementation in all patients treated would be certainly highly desirable, but is not required by Article 83 EPC.

3.4 In addition, pilot studies in humans have established that patients treated with pemetrexed disodium and receiving vitamin B12 supplementation have reduced side effects (page 7, paragraph [0045]).

The OD cannot follow the O1's arguments that in absence of data/information concerning this study, the alleged reduction of side effects with vitamin B12 alone is purely speculative. As mentioned in point 3.3 above, the clinical trials described in the present patent show that vitamin B12 supplementation with pemetrexed reduce severe toxicities by about 25%. In the absence of any evidence from O1 to the contrary, on whom the burden of proof lay, the OD has no reason to doubt the validity of the results of the pilot studies referred to in paragraph [0045].

3.5 With respect to O1's argument that the opposed patent does not sufficiently enable the vitamin B12 derivatives and the folic protein binding agent other than folic acid mentioned in claim 1, the OD wants to make the following comments. All the vitamin B12 derivatives mentioned in claim 1 have vitamin B12 activity. The same applies to the folate analogs of claim 2 which are all folic binding protein binding agents. Therefore, the OD has no reason to doubt that the different vitamin B12 and folate derivatives will behave in the same way in the context of the invention, i.e that each derivative could be substituted one for the other, with the expectation that the same intended result with regard to the reduction of premetrexed toxicity would be achieved.

3.6 Accordingly, the OD takes the view that there is clear and sufficient data in the opposed patent to support the claimed subject-matter.

4 Novelty (Article 100(a) in conjunction with Article 54 EPC)

4.1 O1 argued that the clinical trials reported in the post-published documents D1-D5 which occurred before the earliest priority date of the opposed patent establish prior use that is novelty destroying for the claimed invention.

All the documents D1-D5 (which are post-dated) would make clear that pemetrexed disodium was publicly used in combination with vitamin B12 and folic acid (**what**), the methods of administration (**how**), the center **where** the clinical trials took place and by whom they where performed starting from December 1999 (**when**). Hence, the submitted documents would fully substantiated the public prior use according to established case law (e.g. T93/89).

4.2 As mentioned by O1, a method disclosed by prior public use is regarded as state of the art if the following items can be determined (Guidelines, D-V, 3.1.2):

(I) the date on which the alleged use occurred

(ii) what has been used (the object of the prior use)

(iii) all the circumstances relating to the use, by which it was made available to the public, as for example the place and the form of use.

4.3 The OD shares the point of view of O1 that the first two items were proved. Document D1-D5 make clear that the clinical trial concerning the combination of pemetrexed disodium with vitamin B12 and folic acid (**what**) started in December 1999 (**when**).

As to the circumstances (third item), P has submitted that in the present case the trials were conducted under confidentiality and to prove this P provided new documents D15 and D16. It appears very clearly to the OD that these clinical trials which concern the treatment of cancer were tested in a hospital/clinic setting under the responsibility of a medical practitioner within the frame work of an investigator's agreement provided with confidentiality clauses. It is also clear to the OD that the therapy was not approved or commercialised before the priority date of the opposed patent.

4.4 O1 further argued that the two documents D15 and D16 do not remove doubt on confidentiality as they only purportedly relate to one of the numerous investigator centers for each clinical study. Furthermore, O1 stated that there is no mention of the

patient being bound by confidentiality in D15 and D16. The composition of the opposed patent was administered in hundreds of patients worldwide. In such circumstances, the realistic assumption would be that the therapy which is the subject of a large clinical trial has become part of the public domain, for example, by patients discussing the details of their cancer therapy with other members of the public.

4.5 The OD cannot share this point of view. In line with established case law, the OD considers that in the medical field there is a prima facie assumption that any person involved in a clinical trial is obliged to confidentiality, given the need for patient confidentiality and the need to protect the development and the testing of the medicament (T906/01; T818/93; T152/03).

In the absence of evidence of the contrary, the OD has no reason to doubt that all the agreements between P and the investigators in all centers were provided with confidentiality clauses as illustrated by D15 and D16.

Neither did O1 provide any evidence that the tested combination was made available to a person other than the persons involved in the investigation process.

4.6 However, even assuming that the patient entered in contact with members of the public, there is no evidence to establish that he could effectively disclose the invention to others. Although he was certainly told to be under anticancer therapy, it has not been proven that he was informed about the exact nature of the treatment, and whether he would necessarily have understood it to a level permitting a meaningful disclosure of the invention.

4.7 In this respect, it must be emphasized that the clinical trial H3E-MC-JMCH referred to in D1-D3 which related to a phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma (MPM) was based on a single, randomized, **single-blind** study. According to the generally accepted meaning, a single-blind experiment is a testing procedure in which the investigators do not tell the subjects if they are being given a test treatment or a control treatment. In other words, in the above mentioned clinical trial, the individual patients did not know whether they were being given cisplatin alone or a combination of cisplatin and pemetrexed. The fact that the patients were not aware of the drug used in their cancer therapy has obviously prevented them from disclosing the invention to other persons before the priority date.

4.8 Accordingly, and in the absence of any evidence to the contrary, it is assumed that the two clinical trials reported in the post-published documents D1-D5 concerning the anticancer drug pemetrexed were covered by an obligation of confidentiality which had to extend over the whole medical team for the entire duration of the procedure, as illustrated by D15 and D16. It can be assumed that confidentiality was also imposed on the patient as condition in the informed consent or that he was not informed of all details of the procedure (more particularly in the clinical trial H3E-MC-JMCH).

4.9 Furthermore, claim 1 of the opposed patent which is in second medical use format requires a therapeutic effect on cancer. For a prior public use to have occurred the existence of this anticancer activity needs to have been made available in a public way.

4.9.1 O1 argued that the relevant activity to be taken into account for the assessment of novelty is the reduction of toxicity and not the anticancer activity in view of the well known antitumor properties of pemetrexed. According to O1, it was clear from D2 that supplementation with folic acid and vitamin B12 improved the clinical outcome, the advantage being associated with the possibility to deliver more cycles. One cycle therapy was a 21-day period. The median number of cycles was 6. By consequences, starting in December 1999, all cycles had been completed before the priority date, and before this date, reduction of the toxic effects when pemetrexed was administered in combination with vitamin B12 and folic acid must have been apparent.

4.9.2 The OD does not share this point of view. Claim 1 of the opposed patent relates clearly and unambiguously to the use of pemetrexed in combination therapy with vitamin B12 for inhibiting tumor growth. In the light of the decisions G5/83 and G2/88 the intended therapeutic use on tumor growth mentioned in claim 1 is the limiting feature from which novelty should derive. Consequently, in order to destroy the novelty of this "second medical use" claim the existence of an antitumor activity needs to have been made available to the public, regardless of the effect of vitamin B12 in the claimed combination.

Consequently, O1's arguments based on the fact that the reduction of side effect with vitamin B12 and folic acid was certainly apparent before the priority date become irrelevant.

4.9.3 O1 has not provided any evidence to suggest that the anticancer activity was, or even would have been recognised in the patients receiving the vitamin B12 supplement, folic acid and pemetrexed, in a public way before the effective filing date of the patent.

As mentioned in point 4.3 and 4.5 above, the two clinical trials reported in the post-published documents D1-D5 concerning the anticancer drug pemetrexed were covered by an obligation of confidentiality which had to extend over the whole medical team for the entire duration of the procedure. This means that even if the medical team decided that enough data were available to draw positive conclusions on the efficacy of the combination in the treatment of cancer before the priority date of the patent, the investigators could not render the results available to the public due to their obligation to confidentiality.

4.9.4 The OD is also convinced that the individual patients enrolled in the two clinical trials could not possibly render this information accessible to the public.

The clinical trial H3E-MC-JMCH referred to in D1-D3 related to a phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma (MPM). This clinical trial was based on a single, randomized, **single-blind**, phase III study. In other words, the individual subjects did not know whether they were being given cisplatin alone or a combination of cisplatin and pemetrexed (see point 4.7 above). The individual patients could not know either the results form the other patients. Moreover, even if the individual patients were well aware of the details of the treatment and the drugs administered, it was obviously not possible for them to attribute a potential beneficial effect on tumor growth to pemetrexed in the absence of comparative data. A potential beneficial effect on tumor growth could be due to cisplatin as well. In any case, none of the treated patients enrolled in this large scale clinical trial could possibly establish a direct relationship between a potential beneficial effect of their anticancer treatment and the administration of pemetrexed.

The clinical trial H3-MC-JMDR referred to in document D4 and D5 is an open-label phase II study of pemetrexed with and without folic acid and vitamin B12 supplementation as therapy in malignant pleural mesothelioma (MPM). A total of 64 patients were enrolled. Forty-three patients received vitamin supplementation from December 1999 onward. An open-label trial is a clinical trial in which doctors and participants know which drug is administered. Therefore, the patients enrolled in this clinical trial were fully aware of the drugs that they were taken.

However, the primary outcome of the trial was the tumor response which was measured using CT scan or magnetic resonance imaging scan (D5, page 1557, right-hand column, paragraph 2). Furthermore, the objective tumor measurement is difficult in MPM (D5, page 1558, left-hand column, paragraph 2).

Consequently, since the inhibition of tumor growth as claimed in the patent had to be assessed by measuring the size of the tumor by CT scan or MRI, the OD can only conclude that the individual patients enrolled in the phase II clinical trial referred to in D4 and D5 were unable to determine alone the effect of a combination of pemetrexed with vitamin B12/acid folic on the tumor growth. Therefore the patients of this clinical trial could not possibly render the results of their treatment available to the public.

4.9.5 In addition, the OD share the P's point of view that a clinical trial is not a guarantee of success. The therapeutic effect of a medicament tested cannot be predicted and conclusions can only be drawn at the end of a phase III clinical trial, in the present case after the priority date of the patent.

4.10 For these reasons, the OD arrives at the conclusion that the evidence provided in the course of the proceedings is no sufficient to establish that the subject-matter of claim 1 (and its dependent claims 2-11) was rendered available to the public in such a way that it was comprised in the state of the art.

The same applies to the granted claim 12 (and dependent claims 13-14) which relates to a product per se for use in the inhibition of tumor growth. Since the patent has been granted before the 13th December 2007, the provision of Article 54(5) EPC 2000 does not apply (Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000, Article 1: points 1 and 3). However, claim 12 amounts to a first medical use in the sense of Article 54(5) EPC 1973, for which at least one therapeutic activity must have been disclosed to object for lack of novelty. This appeared not to be the case for the same reasons as developed here above for claim 1.

4.11 Based on the above, the OD is of the opinion that the alleged prior use of the claimed combination for the treatment of cancer was not made available to the public and is not state of the art within the meaning of Article 54(2) EPC.

5 Inventive step(Article 100(a) in conjunction with Article 56 EPC)

5.1 Document D28, which constitutes the closest prior art, is a scientific article in which the action and toxicities of antifolate anticancer agents, including pemetrexed is discussed. D28 discloses the antitumor properties of pemetrexed (MTA) as well as its toxicity. This toxicity is correlated to an increase in homocysteine levels (page 9, left-hand column, paragraph 1). D28 further teaches that any functional deficiency either in B12 or folate will result in an increase in the plasma level of homocysteine (page 8, right-hand column).

5.2 The problem to be solved by the present invention is to reduce the toxicity associated with the administration of pemetrexed disodium in cancer patients.

The proposed solution is to use vitamin B12 alone or in association with folic acid.

5.3 The OD is convinced that the above-mentioned problem was solved in the light of the experimental data described on paragraphs [0034] to [0056] of the patent in suit (see point 3 above "insufficiency of disclosure").

5.4 During oral proceedings, O1 has argued lack of inventive step based on D28 taken alone or in combination with D9 in view of the general knowledge D13.

D28 teaches that the toxicity of pemetrexed is correlated to an increase in homocysteine plasma levels; said increase of homocysteine plasma level being known to be correlated with vitamin B12 deficiency. Consequently, the solution to the problem of the toxicity of pemetrexed, i.e. the administration of vitamin B12 was thus obvious in view of D28 based on the disclosure of pages 8-9 and Fig.8 (see point 5.1 above).

Alternatively, according to O1 D28 can be combined with D9 (reference 17 of D28). D9 discloses a study concerning the problem of toxicity of pemetrexed. Neutropenia, thrombocytopenia, mucositis and diarrhea are mentioned as toxic side effects related to high level of homocysteine. The skilled person starting from D28/D9 and knowing that the pemetrexed toxicity is related to homocysteine would have been prompted by D13 to use vitamin B12 to lower the homocysteine blood level, and thus, the toxic effects thereof, since D13 teaches that an improved vitamin B12 status normalizes homocysteine levels in blood, which is in fact common general knowledge. According to O1, by administering vitamin B12 to correct homocysteine level and thereby the toxic effects of pemetrexed, the opposed patent did nothing more than apply standard knowledge.

5.5 The OD cannot follow this line of arguments.

D9 is an abstract which relates to pemetrexed (LY231514 or MTA) and the relationship of vitamin metabolite profile to toxicity. The abstract reports that three vitamin metabolites were measured: homocysteine, cystathioine and methyl malonic acid. D9 reports that there was a strong correlation between baseline homocysteine levels and the development of number toxicities such as neutropenia, thrombocytopenia, mucositis or diarrhea. Toxicity was seen in all patients with increased level of homocysteine. No correlation between those toxicities and the remaining pre-specified predictors, namely methylmalonic acid (MMA) and cystathionine was seen.

The strong correlation between homocysteine level and pemetrexed toxicity is also reported in other documents, for example in D10, D26 or D27. It was therefore well established, at the priority date of the patent, that the toxicity of pemetrexed is correlated to an increase in homocysteine plasma levels.

However, it appears that vitamin B12 is not the only marker of an increased level of homocysteine.

As can be appreciated from D8 and D13, homocysteine requires folate to convert to methionine. If no folate is present then homocysteine levels rise. Cystathionine is the deficiency marker for vitamin B6. If vitamin B6 is deficient then cystathioine levels rise. Methyl malonic acid (MMA) is the deficiency marker for vitamin B12. However, vitamin B12 is also involved as a cofactor in the conversion of homocysteine to methionine. Thus, in some cases a vitamin B12 deficiency will also cause increased homocysteine as well as increased MMA.

This is in line with the teaching of D29 where it can be seen that folate deficiency is only associated to elevated serum level of homocysteine, whereas vitamin B12 deficiency is associated to elevation of serum level homocysteine and MMA (page 242, Table VII; page 244, left-hand column paragraphs 2-4).

The OD is therefore of the opinion that since D9 teaches that there is no correlation between pemetrexed toxicity and the marker for vitamin B12 deficiency (MMA), the skilled person would have concluded that vitamin B12 was not involved in the toxicity observed in pemetrexed treatment. He would thus have found no motivation to use vitamin B12 given that the known marker for its deficiency was uncorrelated.

Consequently, starting from D28, the skilled person faced with the problem of reducing pemetrexed toxicity would have ruled out the involvement of vitamin B12 in view of the teaching of D9 and therefore would not have used this vitamin to reduce said toxicity.

The OD considers that the skilled person would have rather used folic acid since in the absence of correlation between the pemetrexed toxicity and MMA as reported in D9, the elevated level of homocysteine described in said document would have been recognised as the marker for folate deficiency. In addition, the solution to the problem of pemetrexed toxicity has been already proposed in D12 and D26 as being the combined treatment of pemetrexed with folic acid.

5.6 During the procedure, additional arguments against inventive step were based on the combination of documents D19 with D23; D21 (or D20 or D22) in combination with the skilled person's common technical knowledge.

Documents D20-D22 describe the increase of the antitumor effect of the folic antagonist methotrexate when combined with vitamin B12. These documents however do not address the problem of the present invention, namely the toxicity of the antifolate drugs.

Document D19 relates to the use of vitamin B12 as a mean of protecting methotrexate hepatotoxicity. However, liver toxicity is generally not associated with pemetrexed treatment (see the opposed patent, Table 1 or D9). In the clinical phase I study of pemetrexed reported in D23, only one patient out of thirty two had hepatic toxicity.

5.7 In view of the foregoing, it is the OD's opinion that the subject-matter of the patent in suit does involve an inventive step and thus fulfills the requirements of Article 56 EPC.

6 DECISION

In view of the arguments presented above, the grounds for opposition do not prejudice the maintenance of the patent unamended.

The opposition is therefore rejected and the patent is maintained as granted (Article 101(2) EPC).

Article 106
Decisions subject to appeal

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

(2) A decision which does not terminate proceedings as regards one of the parties can only be appealed together with the final decision, unless the decision allows a separate appeal.

(3) The right to file an appeal against decisions relating to the apportionment or fixing of costs in opposition proceedings may be restricted in the Implementing Regulations.

Rule 97
Appeal against apportionment and fixing of costs

(1) The apportionment of costs of opposition proceedings cannot be the sole subject of an appeal.

(2) A decision fixing the amount of costs of opposition proceedings cannot be appealed unless the amount exceeds that of the fee for appeal.

Rule 98
Surrender or lapse of the patent

The decision of an Opposition Division may be appealed even if the European patent has been surrendered in all the designated Contracting States or has lapsed in al those States.

Article 107
Persons entitled to appeal and to be parties to appeal proceedings

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

Article 108
Time limit and form

Notice of appeal shall be filed in accordance with the Implementing Regulations, at the European Patent Office within **two months** of notification of the decision. Notice of appeal shall not be deemed to have been filed until the fee for appeal has been paid. Within **four months** of notification of the decision, a statement setting out the grounds of appeal shall be filed in accordance with the Implementing Regulations.

Further information concerning the filing of an appeal

(a) The appeal is to be filed with the European Patent Office either at its seat in Munich, at its branch at The Hague or at its Berlin sub-office. The postal addresses are as follows:

(i) European Patent Office
80298 Munich
GERMANY
(Fax : +49 89 2399 4465)

(ii) European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
(Fax : +31 70 340 3016)

(iii) European Patent Office
10958 Berlin
GERMANY
(Fax : +49 30 25901840)

(b) The notice of appeal must contain the name and address of the appellant in accordance with the provisions of Rule 41(2)(c) EPC, an indication of the decision impugned, and a request defining the subject of the appeal. In the statement of grounds of appeal the appellant shall indicate the reasons for setting aside the decision impugned, or the extend to which it is to be amended, and the facts and evidence on which the appeal is based (R. 99(1) and (2) EPC). The notice of appeal and any subsequent submissions stating the grounds for appeal must be signed (R. 50(3) EPC).

(c) Notice of appeal can be filed in accordance with Rule 1 and Rule 2(1) EPC, by delivery by hand, by post, or by technical means of communication. The filing has to comply with the details and conditions and, where appropriate, any special formal or technical requirements laid down by the President of the European Patent Office (R. 99(3) EPC).

(d) The fee for appeal is laid down in the Rules relating to Fees. The equivalents in the national currencies in which the fee for appeal can be paid are regularly published in the Official Journal of the European Patent Office under the heading "Guidance for the payment of fees, costs and prices".