Bundespatentgericht
Tribunal fédéral des brevets
Tribunale federale dei brevetti
Tribunal federal da patentas
Federal Patent Court

O2018_003

Judgment of 15 October 2019

Court Composition

Instructing Judge Dr. iur. Daniel M. Alder,
Judge Dr. rer. nat., Dipl. Chem. Roland Dux (judge rapporteur),
Judge Dipl. Chem.-Ing. ETH Marco Zardi,
First law clerk lic. iur. Susanne Anderhalden

Parties to the Proceedings

Sandoz Pharmaceuticals AG, Suurstoffi 14, CH 6343 Rotkreuz,

represented by Attorney at Law Dr. iur. Markus Wang, Bär & Karrer AG, Brandschenkestrasse 90, 8027 Zurich, advised on patent law by Christoph Fraefel, Schaad Balass Menzl & Partner AG, Dufourstrasse 101, 8034 Zurich, Switzerland

Plaintiff

v e r s u s

Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, 46285 Indiana, USA

represented by Attorney at Law Dr. iur. Christian Hilti and Attorney at Law Dr. iur. Demian Stauber, Rentsch Partner AG, Bellerivestrasse 203, Postfach, 8034 Zurich, advised on patent law by Andrea Carreira, Rentsch Partner AG, Bellerivestrasse 203, Postfach, 8034 Zurich, Switzerland

Defendant

Object

Patent Revocation; Pemetrexed

The Federal Patent Court considers:

History of the Case

1

On 1 February 2018, Plaintiff filed the present action for revocation of the patent with the following prayer for relief (act. 1):

"1. That the invalidity of the Swiss part of EP 1 313 508 be found.

2. Everything with costs and expenses to be borne by Defendant, including the expenses incurred by the patent attorney."

2

In its statement of defense of 3 May 2018, Defendant requested that the action be dismissed and that all costs and expenses be borne by Plaintiff (act. 7).

3

At the preparatory hearing of 9 July 2018, no agreement could be reached (act. 18).

4

The reply was filed on 24 September 2018 with no changes to the prayer for relief (act. 22).

5

On 30 October 2018, Plaintiff submitted new facts and evidence (act. 26).

6

In its rejoinder of 14 November 2018, Defendant filed the following alternative requests (act. 30):

"1) Alternative request 1

1. 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 and after the administration of vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin.

2) Further alternative request 2

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after administration of the vitamin B12 or pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof.

3) Further alternative request 3

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after administration of the vitamin B12 or pharmaceutical derivative thereof and the medicament is to be administered after the folic binding protein binding agent, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof.

4) Further alternative request 4

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof.

5) Further alternative request 5

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with the vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof, and wherein the vitamin B12 or the pharmaceutical derivative thereof is to be administered in an amount of 500 µg to 1500 µg.

6) Further alternative request 6

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with the vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof, and wherein the vitamin B12 or the pharmaceutical derivative thereof is to be administered as an intramuscular injection with 500 µg to 1500 µg.

7) Further alternative request 7

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with the vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, and wherein the administration of the vitamin B12 or a pharmaceutical derivative thereof is to be repeated every 6 to 12 weeks, und said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and the folic binding protein binding agent being selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof, and wherein the vitamin B12 or the pharmaceutical derivative thereof is to be administered as an intramuscular injection with 500 µg to 1500 µg.

8) Further alternative request 8

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with the vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and wherein the folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof, and wherein the vitamin B12 or the pharmaceutical derivative thereof is to be administered as an intramuscular injection with approximately 1000 µg.

9) Further alternative request 9

1. 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 and a folic binding protein binding agent, and wherein the medicament is to be administered after pretreatment with the vitamin B12 or a pharmaceutical derivative thereof followed by the folic binding protein binding agent, and wherein the medicament is to be administered after the folic binding protein binding agent, and wherein the administration of the vitamin B12 or a pharmaceutical derivative thereof is to be repeated every 6 to 12 weeks, und said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and the folic binding protein binding agent being selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof, and wherein the vitamin B12 or the pharmaceutical derivative thereof is to be administered as an intramuscular injection with approximately 1000 µg."

7.

On 12 December 2018, Defendant filed a statement regarding the new facts and evidence submitted by Plaintiff (act. 34).

8.

On 14 December 2018, Plaintiff filed a statement regarding the rejoinder with the amended prayer for relief that the alternative requests of Defendant should also be dismissed (act. 35).

9.

On 24 January 2019, Defendant submitted new facts and evidence (act. 39). Plaintiff's statement regarding these new facts and evidence was filed on 8 February 2019 (act. 41).

10.

On 12 March 2019, Judge Roland Dux delivered an expert judge's opinion (act. 42).

11.

Subsequently, the parties were summoned to the main hearing on 17 June 2019 (act. 44).

12.
The parties submitted their statements on the expert judge's opinion by pleadings of 12 April 2019 (Plaintiff, act. 49) and 7 May 2019 (Defendant, act. 50), respectively.

13.
The main hearing took place on 17 June 2019 (act. 61).

Procedural Matters

14.
Plaintiff is a Swiss stock corporation having its registered office in Switzerland. Defendant is an American company having its registered office in the United States. The facts of the case are therefore international. Based on Art. 1 para. 2 of the Swiss Private International Law Act (*Bundesgesetz über das Internationale Privatrecht - IPRG*) in conjunction with Art. 22 para. 4 of the Lugano Convention and Art. 26 para. 1 lit. a of the Swiss Patent Court Act (*Patentgerichtsgesetz - PatGG*), jurisdiction lies with the Swiss Federal Patent Court.

Pursuant to Art. 110 para. 1 of the Swiss Private International Law Act (IPRG), Swiss law is applicable.

Substantive Matters

15. The Patent in Suit
The Swiss part of the European patent EP 1 313 508 B1, which is owned by Defendant (act. 1_5; the "Patent in Suit"), is at issue. The patent in suit was filed on 15 June 2001, claiming three US priorities of 30 June 2000, 27 September 2000 and 18 April 2001. The patent was granted on 18 April 2007.

The patent in suit relates to a composition containing an antifolate and a methylmalonic acid lowering agent.

16.
The granted patent in suit contains the independent claims 1 and 12 as well as the claims 2 - 11 dependent on claim 1 and the claims 13 and 14 dependent on claim 12.

1. *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 pharmaceutical derivative of vitamin B12*

being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin.

12. *A product containing pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo- 10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and, optionally, a folic binding protein binding agent selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically available salt or ester thereof, as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumor growth.*

17. Foreign Proceedings

Germany:

In its judgment of 17 July 2018 (act. 26_52), the German Federal Patent Court revoked the German part of the European patent EP 1 313 508 B1 in the action for revocation brought by Hexal AG, Strada AG and ratiopharm on the grounds of lack of an inventive step of claim 1 and of auxiliary requests 1 to 9. The court left open whether novelty existed (act. 26_52, p. 17).

Netherlands:

In its judgment of 16 January 2019 (act. 39_57), the Court of The Hague dismissed Sandoz's action for revocation and considered the claims of the European patent EP 1 313 508 B1 to be novel and inventive (act. 39_57, E. 4.7, 4.27).

United States:

In its judgment of 12 January 2017 (act. 7_3), the US Court of Appeals for the Federal Circuit considered the corresponding US 7,772,209 to be novel and inventive and dismissed Teva's action for revocation.

In the *inter partes* review proceedings (act. 7_4) before the Patent Trial and Appeal Board (PTAB) of the USPTO, the corresponding US 7,772,209 was also considered patentable.

Japan:

In 2015, Sawai Pharmaceutical Co. initiated revocation proceedings against the Japanese equivalent of the patent in suit, in which three other companies intervened. The JPO maintained the patent. This decision was upheld by the Japan Intellectual Property High Court. Plaintiff was not a party to the proceedings.

Opposition Proceedings before the European Patent Office:

The patent in suit was the subject of opposition proceedings before the European Patent Office. In its decision of 18 November 2010 (act. 7_36), the Opposition Division concluded that the claims granted were novel and inventive.

18. Technical Field

The patent in suit concerns the field of cancer treatment. Antifolates have already been used for cancer therapy in the past. Antifolates are analogous of folic acid, which interfere with DNA synthesis by inhibiting the corresponding enzymes, thereby preventing cell division and thus the growth of cancer cells. However, due to these cytotoxic effects, antifolates have serious disadvantages.

According to the patent in suit, it was *"[s]urprisingly [...] discovered that certain toxic effects such as mortality and non-hematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent as vitamin B12, without adverse adversely affecting therapeutic efficacy"* [0005].

The biochemical processes (cf. also E. 21) in which folic acid and/or vitamin B12 are involved were widely discussed by both parties. It is undisputed that these different processes interfere with each other and therefore influence each other.

Therefore, due to their participation in these biochemical processes, the substances homocysteine and methylmalonic acid (MMA), which act as markers, are particularly relevant in addition to the reduced folates.

19. The Person Skilled in the Art

Plaintiff regards the skilled person as a team of specialists, including in particular a medicinalal chemist or a pharmacologist specializing in the mechanisms of action of antifolates with many years of professional experience in the research of antifolates for the treatment of cancer, and, where appropriate, a physician specializing in oncology with many years of experience in the chemotherapeutic treatment of cancer patients with anti-cancer agents such as antifolates (act. 1, margin no. 50).

Defendant argues that the skilled person can only be a medical oncologist who has experience in the treatment of cancer patients with chemotherapeutic agents, including antifolates, and in dealing with the toxicities associated with such chemotherapy, and who has pharmacological knowledge. Alternatively, the person skilled in the art could be a researcher with experience in the use of antifolates for the treatment of cancer and an understanding of the clinical use of antifolates in cancer (act. 7, margin no. 140).

The mere fact that the patent in suit is a specific chemical compound used to treat cancer and that the treatment of toxicities is a relevant aspect of the invention means that the skilled person must be a team, consisting of a chemist, a pharmacist and an oncologist with experience in the treatment of cancer and in the mechanisms of action of antifolates.

20. Novelty in Relation to the "*Worzalla*" Document

Plaintiff argues that claims 1 - 8 and claims 12 - 14 of the patent in suit are not novel in relation to *Worzalla* (act. 1_12). This document examined the influence of folic acid on the toxicity and efficacy (on antitumor activity) of pemetrexed (administered as disodium salt) (act. 1, margin no. 76). For this purpose, the lab mice were fed with a standard diet or with a folate-deficient diet (act. 1, margin no. 77). Not only folic acid but also vitamin B12 was administered with this standard food "Purina Chow #5001" (act. 1, margin nos. 79, 87).

Defendant does in particular not see any disclosure of vitamin B12 (act. 7, margin no. 148) in *Worzalla* (act. 1_12). In addition, none of the documents act. 1_13 or act. 1_14 or act. 1_15 could support the arguments with regard to the administration of vitamin B12 (act. 7, margin no. 151). Moreover, even if *Worzalla* disclosed vitamin B12, feeding without quantity control would not be an "administration" in the sense of a combination therapy (act. 7, margin no. 160).

Assessment of Novelty in Relation to the "*Worzalla*" Document:

For the assessment of novelty in relation to *Worzalla* (act. 1_12), it is primarily the disclosure content of this document that is relevant. It is undisputed that *Worzalla* does not show any direct disclosure of vitamin B12 or a pharmaceutical derivative thereof. It must therefore be examined whether there is an implicit disclosure of vitamin B12 in *Worzalla*. According to established case law of the European Patent Office the requirements for the existence of an implicit disclosure have to be set high. In particular, the person skilled in the art must be able to derive the subject matter directly and unambiguously from the relevant document.[1]

Worzalla discloses "Purina Chow #5001". In addition to folic acid, the product information (act. 1_13 and act. 1_14) entitled "Laboratory Rodent Diet 5001" also mentions vitamin B12. However, even taking into account the information contained in the document "Lab-Diet-Advanced Protocol" (act. 1_15), Plaintiff's view, namely that the aforementioned "Purina Chow #5001" in *Worzalla* clearly contains vitamin B12 (and folic acid), cannot be followed. Apart from the fact that neither the designations "Purina Chow" and "Laboratory Rodent Diet" nor the designations of the numbers "#5001" and "5001" are identical, it could not be proven directly and conclusively that "Purina Chow #5001" and "Laboratory Rodent Diet 5001" (PMI or LabDiet) represent the same products or have the same composition.

Nor do the references to act. 1_16 and act. 1_17 convincingly show that any standard dietary food for rodents directly and unambiguously contained vitamin B12 at the time of filing.

Thus, there is no implicit disclosure of vitamin B12 or folic acid due to "Purina Chow #5001" in *Worzalla*.

[1] Cf. T 95/97, T 51/10.

Thus, at least the feature "*administered in combination with vitamin B12 or a pharmaceutical derivative thereof*" of claim 1 or "*containing vitamin B12 or a pharmaceutical derivative thereof*" of claim 12 is not disclosed in *Worzalla*, such that claims 1 - 8 and 12 - 14 are novel in relation to *Worzalla*.

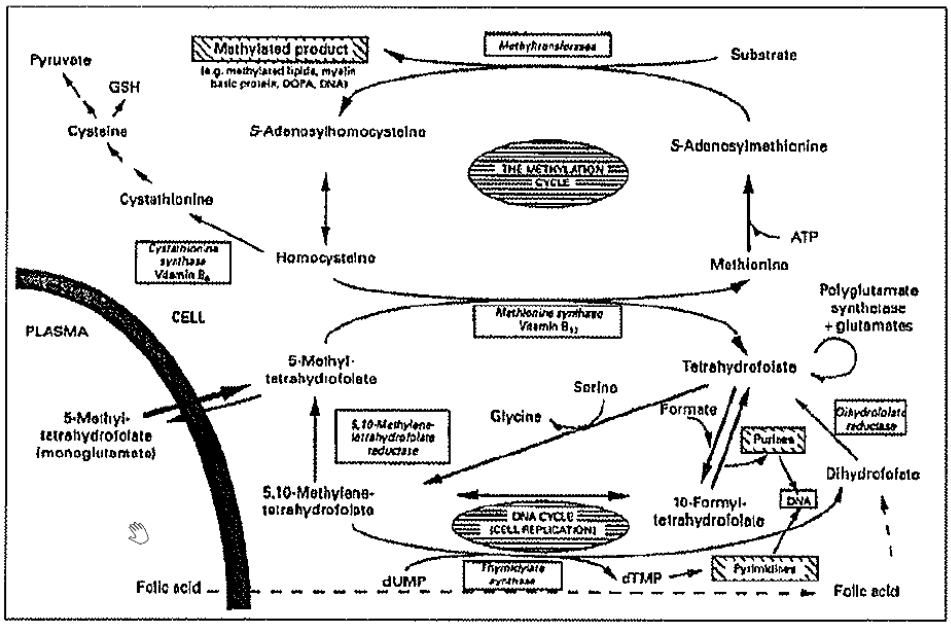
For this reason, the question of the extent to which *Worzalla* discloses a therapeutic use against tumor growth may also remain open.

21. Inventive Step

Plaintiff argues that all claims lacked inventive step in relation to *Niyikiza* et al. (act. 1_19), in relation to the "IBIS Guide to Drug-Herb and Drug-Nutrient Interactions" (act. 1_27; hereinafter referred to as "*IBIS*") and in relation to "Antifolate Drugs in Cancer Therapy" (act. 1_28; hereinafter referred to as "*Jackman*"). Furthermore, in the discussion (act. 1, margin no. 194) of the decision of the European Patent Office, Plaintiff argues that all claims are not inventive in relation to "An Overview of Folate Metabolism" (act. 1_7; hereinafter referred to as "*Calvert*").

Defendant rejects the arguments of Plaintiff and affirms the existence of an inventive step for all claims.

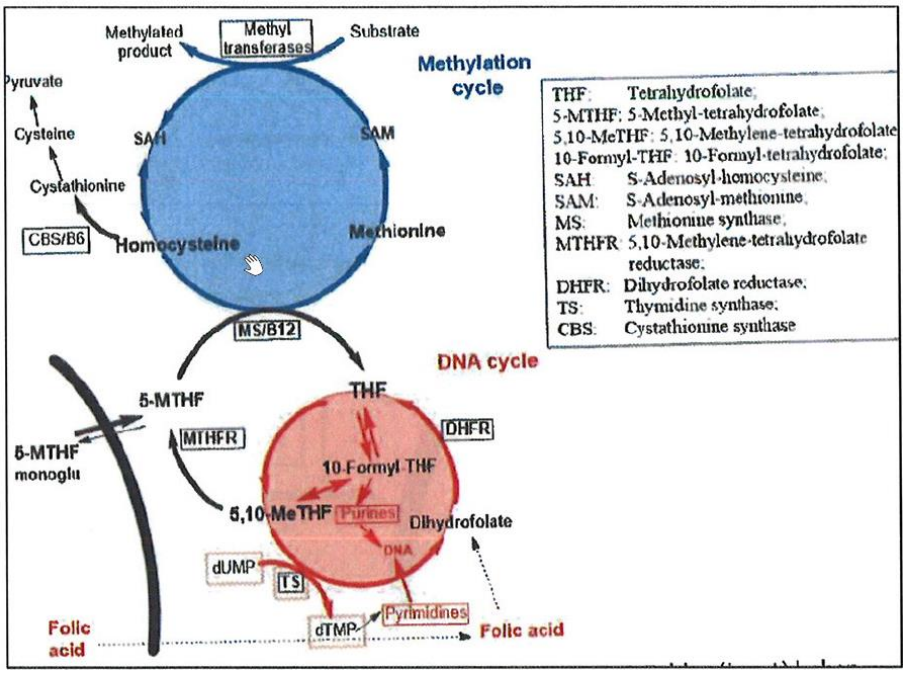
The biochemical processes involving folic acid and vitamin B12 are essential for the assessment of an inventive step. Both Plaintiff and Defendant refer to the following figure (act. 1_10, p. 442, Fig. 1):



It is undisputed that pemetrexed is a multi-target antifolate (MTA) which, according to the patent in suit [0002-0004], inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT). In the above figure, TS and DHFR are represented by rectangles at the bottom in the middle and at the bottom on the right, respectively. GARFT is part of the purine cycle (not explicitly shown above). All these enzymes are essential for cell proliferation and are part of the "DNA cycle". In contrast to pemetrexed, previously developed antifolates do not block all enzymes, but only isolated ones: methotrexate is a DHFR inhibitor, while Lometrexol and LY309887 are GARFT inhibitors.

It is also undisputed that vitamin B12 is necessary to maintain the activity of the vitamin B12-dependent enzyme methionine synthase. Methionine synthase is represented by a rectangle in the middle of the figure above. In the "methylation cycle", homocysteine and 5-methyltetrahydrofolate (5-MTHF) are converted to methionine and tetrahydrofolate (THF). It is also undisputed that vitamin B12 only plays a role in the methylation cycle. Vitamin B12 is a co-factor, i.e. it is not consumed during the reaction.

The representation of Defendant (act. 34, margin no. 31) is a representation based on act. 1_10, which schematically shows the methylation cycle and the DNA cycle highlighted in color:



It is also evident in both figures that these two cycles do not exist isolated from each other, but are connected to each other via THF or 5-MTHF. THF is accessible via the methylation cycle from 5-MTHF, via DHFR from dihydrofolate, which in turn can be formed from 5,10-MTHF via TS or alternatively from folic acid (originating from the cell or plasma) as well as from 10-formyl-THF. Furthermore, 5-MTHF can be obtained from 5,10-MTHF and 5-MTHF (monoglutamate). On the other hand, vitamin B12 is not directly involved in the DNA cycle, which is inhibited by pemetrexed as an antifolate, with the aim of preventing cancer cell growth.

If the methylation cycle stops, 5-MTHF is not converted to THF. This situation is referred to as the "methyl trap". In addition, in this case, homocysteine is not converted to methionine, so that the homocysteine level is increased.

Homocysteine, however, is regarded as a non-specific marker, whereas methylmalonic acid is considered a specific marker for vitamin B12.

Because antifolates not only hinder the proliferation of cancer cells but also of healthy cells, they lead to toxic side effects.

22. Inventive Step in Relation to the Document Niyikiza et al. ("*Niyikiza*", act. 1_19)

According to Plaintiff, *Niyikiza* (act. 1_19) described a study in which the side effects caused by pemetrexed were investigated in phase II patients with tumors of the colon, breast and pancreas (act. 1, margin no. 104). The study of homocysteine levels in *Niyikiza* revealed a link between severe pemetrexed toxicity and elevated homocysteine levels prior to treatment (act. 1, margin no. 107). *Niyikiza* concerned the same technical field as the patent in suit.

Niyikiza differed from the patent in suit in that an additional administration of vitamin B12 was not disclosed (act. 1, margin no. 109).

Plaintiff submits that it was in accordance with the common general knowledge that increased homocysteine levels are caused by a deficiency in folic acid and a deficiency in vitamin B12 and refers to the documents act. 1_20, act. 1_21 and act. 1_22 as proof thereof.

It was also part of the common general knowledge that patients with elevated homocysteine levels were administered a combination of folic acid and vitamin B12 to reduce homocysteine (act. 1, margin no. 122). As evidence, Plaintiff cites act. 1_22, act. 1_23 and act. 1_24. In particular, Plaintiff considers this to be established by a recommendation on page 1278 of act. 1_20 (act. 1, margin no. 123).

According to Plaintiff, the person skilled in the art would assume that the patients with elevated homocysteine levels examined in *Niyikiza* suffered either from a folic acid deficiency or from a B12 deficiency. Consequently, without the need for an inventive step, the skilled person would always be induced to administer folic acid together with vitamin B12. It was therefore obvious that the skilled person would administer folic acid together with vitamin B12 to a patient with increased homocysteine levels (act. 1, margin no. 131).

Defendant disagrees with Plaintiff and argues that, while *Niyikiza* (act. 1_19) statistically evaluated the metabolites homocysteine, cystathionine and methylmalonic acid with regard to the frequency of the resulting toxicity, it did not report a correlation of the vitamin B12 marker methylmalonic acid (act. 7, margin nos. 179 - 180).

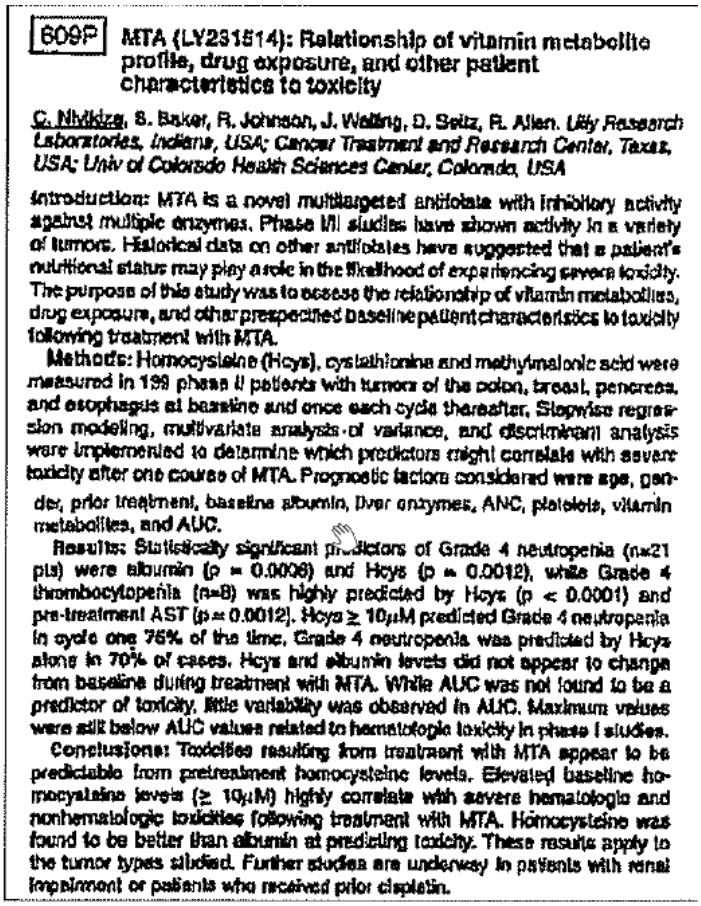
In addition, the cited documents act. 1_20, act. 1_21 and act. 1_22 related to the cardiovascular system and document act. 1_24 to fetal malformations and thus to other medical fields (than that of cancer treatment). Defendant emphasizes that Plaintiff ignored the fact that, in cardiovascular diseases, homocysteine is regarded as the cause of the problem, whereas homocysteine was regarded as a marker with no causal relationship in the use underlying the invention (act. 7, margin no. 182). In addition, Plaintiff ignored the fact that homocysteine was a non-specific marker for folic acid status and vitamin B12 and B6 status, while malonic acid was the only specific marker for vitamin B12 (act. 7, margin no. 183). With regard to the passage in act. 1_20 cited by Plaintiff as support (act. 1, margin no. 123), Defendant states that this recommendation was merely a vague summary of the vitamin combination, the addition of which seems to be useful because it probably ensures full responsiveness to folic acid (act. 7, margin no. 186).

Defendant further argues that *Niyikiza* (act. 1_19) did not disclose more than that homocysteine levels could be regarded as a marker of pemetrexed toxicity. In addition, homocysteine levels were not a cause of toxicity (in contrast to cardiovascular diseases) (act. 7, margin no. 189). Defendant also states that *Niyikiza* (act. 1_19) confirmed the result published in act. 7_10 by the same group of researchers, namely that there is a correlation between homocysteine levels before the start of treatment and the toxicities occurring during pemetrexed treatment (act. 7, margin no. 190) and that act. 7_10 disclosed that no correlation has been found between methylmalonic acid- or cystathionine-levels and subsequent toxicities (act. 7, margin no. 191). The person skilled in the art would have even refrained from administering vitamin B12 because he would have been concerned that this would have a negative effect on treatment with pemetrexed (act. 7, margin no. 198).

Assessment of an Inventive Step in relation to Niyikiza et al. ("*Niyikiza*", act. 1_19):

The object of the patent in suit is to reduce the toxic effects of pemetrexed without adversely affecting the therapeutic efficacy of the antifolate [0005]. The patent in suit solves this object by the use of vitamin B12 or a pharmaceutical derivative thereof, alone or in combination with folic acid.

Niyikiza (act. 1_19) is a very short abstract:



609P **MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity**

C. Niyikiza, S. Baker, R. Johnson, J. Walling, D. Seitz, R. Allen. *Lilly Research Laboratories, Indiana, USA; Cancer Treatment and Research Center, Texas, USA; Univ of Colorado Health Sciences Center, Colorado, USA*

Introduction: MTA is a novel multitargeted antifolate with inhibitory activity against multiple enzymes. Phase I/II studies have shown activity in a variety of tumors. Historical data on other antifolates have suggested that a patient's nutritional status may play a role in the likelihood of experiencing severe toxicity. The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA.

Methods: Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 199 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA. Prognostic factors considered were age, gender, prior treatment, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

Results: Statistically significant predictors of Grade 4 neutropenia (n=21 pts) were albumin ($p = 0.0008$) and Hcys ($p = 0.0012$), while Grade 4 thrombocytopenia (n=8) was highly predicted by Hcys ($p < 0.0001$) and pre-treatment AST ($p = 0.0012$). Hcys $\geq 10\mu M$ predicted Grade 4 neutropenia in cycle one 76% of the time. Grade 4 neutropenia was predicted by Hcys alone in 70% of cases. Hcys and albumin levels did not appear to change from baseline during treatment with MTA. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in phase I studies.

Conclusions: Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels ($\geq 10\mu M$) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA. Homocysteine was found to be better than albumin at predicting toxicity. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

Niyikiza discloses that there is a correlation between pemetrexed toxicity and elevated homocysteine levels prior to treatment. Under "Methods" it is disclosed that homocysteine (Hcys), cystathionine and methylmalonic acid were measured. It is true, however, that *Niyikiza* is silent about the results concerning methylmalonic acid. It is also undisputed that *Niyikiza* does not disclose any vitamin B12 or a pharmaceutical derivative thereof.

The document act. 7_10, which was widely discussed in the discussion of the results of *Niyikiza*, shows that the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured and that it was statistically clarified which predictors (creatinine clearance, albumin levels, liver enzyme levels and vitamin metabolites) could correlate with toxicity. A strong correlation with homocysteine is disclosed. Furthermore, the correlation with cystathionine is discussed. Finally, act. 7_10 discloses *"No correlation between toxicity (CTC grades as defined above) and the remaining pre-specified predictors was seen.":*

LY231514 (MTA): RELATIONSHIP OF VITAMIN METABOLITE PROFILE TO TOXICITY. *C. Niyikiza, J. Walling, D. Thornton, D. Seitz, and R. Allen. Eli Lilly and Company, Indianapolis, IN, and Univ of Colorado Health Science Center, Denver, CO.*

LY231514 (MTA) is a new generation multitargeted antifolate antimetabolite with inhibitory activity against thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. Of a total of 246 patients (pts) in phase II trials treated with MTA (600 mg/m^2 IV over 10 minutes once every 21 days) 118 pts also had vitamin metabolites measured. Because earlier studies with other antifolates had suggested that nutritional status may play a role in the likelihood that a patient will experience severe toxicity, levels of the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured at baseline and once each cycle thereafter. A multivariate statistical analysis of the data was conducted in order to determine which among a set of pre-specified predictors (creatinine clearance, albumin levels, liver enzyme levels, and vitamin metabolites) might correlate with toxicity. There was a strong correlation between baseline homocysteine levels and the development of the following toxicities at any time during the study: CTC Grade 4 neutropenia (67 pts, $p < 0.0001$), Grade 4 thrombocytopenia (13 pts, $p < 0.0001$), Grade 3 or 4 mucositis (8 pts, $p < 0.0003$), and Grade 3 or 4 diarrhea (8 pts, $p < 0.004$). Cystathionine levels did not correlate with hematologic toxicity or mucositis but were moderately correlated with fatigue ($p < 0.04$). Maximum cystathionine levels doubled from baseline during treatment with MTA. No correlation between toxicity (CTC Grades as defined above) and the remaining pre-specified predictors was seen. Toxicity was seen in all patients with homocysteine levels above a threshold concentration of 10 µM. A correlation over time between homocysteine levels and CTC Grade 4 neutropenia and thrombocytopenia and CTC Grade 3 or 4 mucositis was also observed, but only in the first two cycles of treatment. Maximum homocysteine levels did not appear to change from baseline during treatment with MTA.

With regard to this passage, Defendant concludes that act. 7_10 thus disclosed that there was no correlation between methylmalonic acid and toxicity; in other words: that methylmalonic acid was part of the "remaining predictors".

By contrast, Plaintiff concludes that act. 7_10 - after having discussed the vitamin metabolites homocysteine and cystathionine - does not give any indication of a correlation regarding methylmalonic acid (the last of the abovementioned vitamin metabolites); in other words: that the "remaining predictors" merely include creatinine clearance, albumin levels, liver enzyme levels (and thus do not include methylmalonic acid) and suspects that methylmalonic acid levels have not been included in the statistical analysis.

This assessment of Plaintiff is not convincing. Methylmalonic acid is clearly a vitamin metabolite due to the listing (4 lines above the definition of the previously defined predictors).

By mentioning the words "vitamin metabolite" in the *pre-specified predictors* listed in parentheses, methylmalonic acid is thus part of the pre-defined predictors. As mentioned, act. 7_10 only discloses a correlation of homocysteine and cystathionine. For the remaining predicators, no correlation is described according to act. 7_10. Thus, it follows clearly that no correlation is disclosed for the remaining predictor methylmalonic acid, either.

This assessment is also in line with the decision of the Opposition Division of the European Patent Office (act. 7_36 E. 5.5). Furthermore, it should be noted that it is unlikely that methylmalonic acid is mentioned as a vitamin metabolite, which, while being measured, is not statistically evaluated in a scientific paper. Therefore act. 7_10 shows no correlation between toxicity and methylmalonic acid levels.

Since act. 7_10 does not disclose a correlation between toxicity and the methylmalonic acid level, there is no reason for the person skilled in the art to use a methylmalonic acid lowering agent, i.e. vitamin B12, and thus to arrive at the solution to the problem described in the patent in suit.

Thus, all claims are to be regarded as inventive in relation to *Niyikiza* (act. 1_19) as the closest state of the art.

In addition to this, the question of whether the person skilled in the art would always attribute elevated homocysteine levels to a deficiency of folic acid and a deficiency of vitamin B12 should also be considered.

It should be emphasized that homocysteine is considered to be a nonspecific marker, whereas methylmalonic acid is considered to be a specific marker for vitamin B12. In other words, elevated homocysteine levels do not necessarily prove a low vitamin B12 level or even the absence of vitamin B12. Elevated homocysteine levels can also be caused by other factors. Despite all attempts, Plaintiff was unable to demonstrate convincingly that the skilled person would inevitably and "always" treat elevated homocysteine levels with folic acid and vitamin B12. Thus, the person skilled in the art would not necessarily explain elevated homocysteine levels by a folic acid deficiency and a vitamin B12 deficiency.

The documents relied on by Plaintiff concern the cardiovascular system (act. 1_20, act. 1_21 and act. 1_22) and fetal malformations (act. 1_24). It is conclusive that the mechanisms of action in the fields of the cardiovascular system and fetal malformations are not necessarily the same. It follows that the person skilled in the art would give less weight to disclosures from these fields than he would to disclosures from cancer therapy.

The German Federal Patent Court comes to the conclusion (act. 26_52, p. 19, 1st paragraph) *that in the case of pemetrexed administration, blocking the three key enzymes thymidylate synthase (= TS), dihydrofolate reductase (= DHFR) and glycinamide ribonucleotide formyl transferase (= GARFT) in the "DNA cycle" blocks not only this cycle but also the "methylation cycle".* This inference is essential for the conclusion of the German Federal Patent Court that there is no inventive step.

However, this view of the German Federal Patent Court cannot be shared. This, because in case of a blockage of the DNA cycle, the methylation cycle is not blocked. As shown in the above figure (cf. act. 1_10), the 5-MTHF required for the methylation reaction is available both from 5,10-MTHF, which in turn is supplied directly from THF, as well as from plasma as 5-MTHF (monoglutamate). Thus, not all sources of 5-MTHF are derived from the DNA cycle. As a consequence, there is no motivation for the skilled person to administer vitamin B12 in addition to folic acid in antifolate administration in cancer therapy and the folic acid supplementation of pemetrexed is not obvious.

The main points can be summarized as follows:

- *Niyikiza* (act. 1_19) does not disclose vitamin B12 or a pharmaceutical derivative thereof.
- Elevated homocysteine levels prior to treatment do not prove without any doubt a vitamin B12 deficiency.
- The toxicities associated with pemetrexed are caused by high homocysteine levels.
- Even in case of a possible administration of folic acid in the treatment with pemetrexed, an (additional) administration of Vitamin B12 is not to be regarded as given.

- Knowing that folic acid competes with the antifolate and thus reduces the effectiveness of antifolate, it is more than questionable whether the skilled person would have administered folic acid and especially, combined with it, vitamin B12 or a pharmaceutical derivative thereof.

On the basis of the above considerations, Plaintiff's attacks are unsuccessful and all claims must therefore be regarded as inventive in relation to *Niyikiza* (act. 1_19) as the closest state of the art.

23. Inventive Step in Relation to the Document "IBIS Guide to Drug-Herb and Drug-Nutrient Interactions" ("*IBIS*", act. 1_27)

According to Plaintiff, *IBIS* (act. 1_27) discloses the supplementation of methotrexate treatment with folic acid in order to reduce the side effects of methotrexate (act. 1, margin no. 145). In addition, *IBIS* further recommends that vitamin B12 be administered as a supplement, since it acted in combination with folic acid (act. 1, margin no. 146). Plaintiff therefore concludes that *IBIS* thus teaches that vitamin B12 should be added during treatment with methotrexate (act. 1, margin no. 148). The subject matter of the patent in suit differed from the disclosure of *IBIS* only in that the antifolate methotrexate was replaced by the antifolate pemetrexed disodium (act. 1, margin no. 151). It was therefore the objective technical task of the patent to use an alternative antifolate. Pemetrexed had an inhibitory effect on dihydrofolate reductase, *inter alia*, which was also inhibited by methotrexate. Thus, the effect of the anti-folate pemetrexed disodium was based on the same mechanism as that of the antifolate methotrexate. In addition, pemetrexed and methotrexate were structurally closely related. Therefore claim 1, and - by analogy to the remarks made in respect of *Niyikiza* (act. 1_19) - also claims 2 to 11 and claims 12 to 14, did not involve an inventive step (act. 1, margin nos. 152 - 156).

Defendant disagrees with Plaintiff and argues that *IBIS* was a guideline on drug-herb and drug-nutrient interactions and that the passages and references cited by Plaintiff referred exclusively to the treatment of rheumatoid arthritis and not to chemotherapeutic cancer treatment with methotrexate (let alone other antifolates) (act. 7, margin no. 214). Defendant disputes that it constitutes prior art which was accessible to the public on the priority date, since the mere copyright notice was not sufficient to prove this (act. 7, margin no. 215).

Defendant further states that even if *IBIS* had been accessible to the public, the skilled person would not have consulted this prior art because it did not relate to the field of cancer treatment (act. 7, margin no. 216). With regard to the treatment of rheumatoid arthritis, not only was the therapeutic objective completely different, but it was also known that the administration of methotrexate in the treatment of rheumatoid arthritis had a completely different mode of action compared with chemotherapeutic use. Methotrexate is administered at low doses over a long period of time in order to achieve a long-lasting immunosuppressive effect. In contrast, in the treatment of cancer, high doses are administered over a short period of time to maximize the destruction of rapidly dividing tumor cells and minimize toxic effects due to the destruction of healthy cells (act. 7, margin no. 219). In addition, *IBIS* disclosed that the initial assumptions, namely that the effects of methotrexate on folic acid were the cause of its supposed benefit in rheumatoid arthritis as in the case of chemotherapeutic uses, had been abandoned. Rather, it was found that the inhibition of dihydrofolate reductase (DHFR) by methotrexate in folate metabolism, which was relevant for cancer treatment, was expressly not the decisive effect in the treatment of rheumatoid arthritis (act. 7, margin no. 221). Furthermore, in her statement (cf. act. 7_11), Prof. Jackman had emphasized the skilled person's concerns which the skilled person would have had with regard to a contraindication of folic acid with methotrexate (act. 7, margin no. 227). Thus, in *IBIS*, the person skilled in the art would not have found any incentive to carry out a tumor treatment with methotrexate, let alone with pemetrexed, in combination with folic acid or vitamin B12 (act. 7, margin no. 228). Furthermore, the effectiveness of the antifolate is of highest priority in tumor treatment.

Plaintiff disputes the objection that act. 1_27 is not part of the state of the art. According to the affidavit of Dr. M. Stargrove (act. 22_50), the content corresponding to *IBIS* was available on CD as of October 1999, thus being made available to the public and thus being part of the state of the art. Furthermore, Plaintiff disputes that the administration of methotrexate in the treatment of rheumatoid arthritis has a completely different effect than in chemotherapy, since the mode of action of methotrexate is the same both in the treatment of rheumatoid arthritis and in the treatment of tumors.

Assessment of an Inventive Step in Relation to the Document "IBIS Guide to Drug-Herb and Drug-Nutrient Interactions" ("*IBIS*", act. 1_27):

IBIS is a guide to drug-herb and drug-nutrient interactions (act. 1_27).

The first step in determining inventiveness is to clarify whether *IBIS* is a prior art document or not.

In principle, it is correct that a copyright date is not clear evidence that the publication actually took place on that date, but it is certainly an indication of this. Thus, Defendant no longer disputed the concrete claims of Plaintiff (act. 22, margin nos. 232 et seq.) regarding the public accessibility of act. 1_27 before the priority date.

It can therefore be assumed that *IBIS* represents a valid state of the art.

IBIS discloses methotrexate, which is a DHFR inhibitor. While pemetrexed is indeed a DHFR inhibitor, it is additionally also a TS and GARFT inhibitor. Hence, it cannot be concluded that methotrexate and pemetrexed follow the same mechanism of action and that it is therefore obvious *per se* to exchange methotrexate for pemetrexed. This would mean that TS and GARFT inhibition had no influence on the mechanism of action and efficacy of pemetrexed.

The *IBIS* passages cited by Plaintiff relate to the treatment of rheumatoid arthritis. Defendant’s argument that, on the one hand, the mechanisms of action in rheumatoid arthritis and cancer treatment are different and, on the other hand, that the administration is very different in the treatment of rheumatoid arthritis and in chemotherapy is convincing for the following reasons.

The following passage on page 3 in *IBIS* already underlines that also the person skilled in the art did not consider the mechanisms of action in the treatment of rheumatoid arthritis and in the treatment of cancer to be the same.

antirheumatic effect. Most researchers have found that folic acid levels were not relat to parameters of disease activity and concluded that methotrexate does not exert its action in RA primarily by inhibiting dihydrofolatereductase.

The view that the structural similarity between methotrexate and pemetrexed would have been an argument in favor of regarding pemetrexed as an alternative to methotrexate cannot be shared. This, because it is notoriously known to the Court that it is very difficult to predict a pharmaceutical effect solely on the basis of a chemical formula. If in addition it is known that methotrexate and pemetrexed also have different mechanisms of action, this is to be expected even less.

The following passage on page 2 of *IBIS*, which expresses concerns about nutrients during chemotherapy, gives a clear warning to be cautious when administering folic acid, as the administration of folic acid counteracts the efficacy of methotrexate. The last sentence in this passage is also an indication that statements about methotrexate cannot be transferred to other antifolates.

• nutritional concerns with chemotherapy: Since methotrexate's interference with foli acid metabolism is intentional, individuals prescribed this drug for cancer treatment should limit their supplementation of folic acid to a maximum of 400 mcg per day. Consultation with your prescribing physician or other qualified healthcare provider is important because use of folic acid at higher levels might work contrary to the drug's therapeutic intention. However, this caution against folate supplementation does not extend to individuals taking chemotherapeutic agents other than methotrexate.

Thus, based on *IBIS*, the person skilled in the art would not have exchanged the antifolate methotrexate for pemetrexed, and he would certainly not have used vitamin B12 or a pharmaceutical derivative thereof to supplement pemetrexed in cancer therapy.

Thus, all claims are inventive in relation to *IBIS* (act. 1_27) as the closest state of the art.

24. Inventive Step in Relation to the Document "Antifolate Drugs in Cancer Therapy" ("*Jackman*", act. 1_28)

According to Plaintiff, Jackman (act. 1_28) establishes a strong link between antifolate therapy and supplementation of treatment with vitamins, in particular vitamin B12. The chapter on the antifolates "Lometrexol" and "LY309887" proposed the administration of folic acid to human cancer patients in order to reduce the toxicity of the antifolates.

In addition, it was explained that the status of vitamin B12 could significantly influence the severity of toxicity observed during chemotherapy. *Jackman* therefore teaches to supplement the addition of folic acid in antifolate-based cancer therapy with vitamin B12, among others, in order to minimize side effects (act. 1, margin no. 161). According to Plaintiff, the subject matter of the patent in suit differs from the disclosure in *Jackman* only in that the antifolate pemetrexed disodium is used instead of the antifolate "Lometrexol" or "LY309887" (act. 1, margin no. 162). It was thus the objective technical task of the patent in suit to use an alternative antifolate. Lometrexol was very similar in structure to the antifolate pemetrexed and was based on the same mechanism of action, namely the inhibition of dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. LY309887 also had a high structural similarity with pemetrexed and was an inhibitor of glycinamide ribonucleotide formyltransferase.

Thus, in view of the structural similarity and the same mechanism of action, it would have been obvious to the person skilled in the art to replace Lometrexol or LY309887 by the more recent pemetrexed (known to the person skilled in the art e.g. from act. 1_19) as an alternative antifolate. Therefore, claim 1, and - by analogy to the remarks made with respect to *Niyikiza* (act. 1_19) - also claims 2 to 11 and claims 12 to 14 did not involve an inventive step (act. 1, margin nos. 162 - 166).

Defendant disagrees with Plaintiff and submits that Plaintiff cites two chapters in *Jackman* (chapter 8 and chapter 12), but refers only to the chapter which is not related to the antifolate pemetrexed. Chapter 12, which concerns Lometrexol and LY309887 respectively, contains no incentive for the use of a combination therapy of pemetrexed with vitamin B12. On the contrary, the person skilled in the art would deduce from chapter 8 that pemetrexed was an effective antifolate, whose toxicities were controllable and tolerable, and the person skilled in the art would get the incentive to counteract occurring toxicities by reducing the dosage, which was also done in the Phase II studies described in *Jackman*. Thus, no co-therapy was suggested (act. 7, margin nos. 232 - 236).

Defendant states that the mouse studies described in section 2.6 were problematic compared to humans due to the differences in systemic thymidine and folate levels and therefore had little or no prognostic value (act. 7, margin no. 238).

It was alarming that during pre-treatment with folic acid massively increased pemetrexed doses would have to be administered in order to achieve the same antitumor effect - even in the highly sensitized tumor cells. However, higher pemetrexed doses would have a negative effect on the kidneys ("kidney toxicity"). Pre-treatment with folic acid would not protect the kidneys from the toxicity of pemetrexed, instead the longer residence time of pemetrexed would probably worsen the kidney function and lead to worsening of the observed toxicities (act. 7, margin no. 241).

It was misleading and wrong to say that the person skilled in the art would consider the information in chapter 12 to be relevant for treatment with pemetrexed - for example due to the alleged structural similarity of lometrexol and pemetrexed. According to Defendant, the person skilled in the art would *a priori* attribute more relevance to the chapter on pemetrexed for the topic of treatment with pemetrexed, especially since he could explicitly infer from chapter 8 that the metabolic effects of pemetrexed differed from those of LY309887 (act. 7, margin no. 245).

Plaintiff disagrees with Defendant’s argument that folic acid impaired the efficacy of pemetrexed and it was by no means contraindicated (act. 22, margin nos. 68 et seq. with reference to act. 1_28 and act. 1_12). In addition, Plaintiff argues that the person skilled in the art would derive from section 2 of chapter 8 of act. 1_28 (corresponding to act. 22_43) that in a mouse study the toxicity of pemetrexed was significantly more pronounced in the group with the low-folate diet than in mice to which sufficient folic acid had been administered, such that it could be concluded that the administration of folic acid reduced the toxicity / adverse effects of pemetrexed without negatively affecting its efficacy (act. 22, margin nos. 199 - 205). Plaintiff also objects to the argument that the skilled person would have reduced the dosage of pemetrexed in order to reduce the toxicity, because this would evidently have resulted in a reduced antitumor effect. He would have rather pursued the combination therapy of pemetrexed and folic acid clearly recommended in *Jackman* (act. 1_28) than to accept a reduced effectiveness of the antifolate, since the administration of folic acid would have reduced the toxicity while even slightly improving the antitumor effect (act. 22, margin no. 206). Plaintiff derives from the reference in the patent in suit, paras. [0034] to [0043], from act. 7_21 of Defendant, and based on act. 22_41 and act. 22_33 that the results of the mouse studies could also be transferred to humans (act. 22, margin nos. 208 - 213).

Based on the biochemical expert knowledge, the person skilled in the art was aware that functional folic acid must be present in the cell for the reduction of toxicity, i.e. folic acid in the form of THF, and not in the form of 5-MTHF (as in the so-called "methyl trap"; act. 22, margin no. 39).

Defendant discusses in detail Fig. 2 of *Worzalla*, which is said to be identical to Fig. 4 in *Jackman*, to show that in the case of administration of pemetrexed with folic acid the decrease in toxicity would only be achieved at the expense of efficacy and would require much higher dosages, which in turn would pose an increased risk that other side effects would occur that could not be reduced or neutralized by folic acid, such as kidney damage. However, since 100% tumor inhibition without folic acid would already be achieved at significantly lower doses and thus without lethality, the person skilled in the art could use a dose range without lethality and with maximum inhibitory effect (act. 30, margin no. 88).

Plaintiff disagrees with this new line of argument of Defendant by stating that Fig. 2 from *Worzalla* (or the corresponding Fig. 4 from *Jackman*) showed nothing other than that folic acid supplementation allowed an increase in the dosage of pemetrexed to more than 30 mg/kg without this dose being lethal for the test animals. In addition, Fig. 2 showed that tumor inhibition of 100% would be achieved at said dose. Without folic acid supplementation, however, said dose of 30 mg/kg would be lethal (indicated by the vertical line at said dose, which extended up to 100% lethality).

In particular, Plaintiff repeatedly argues that *Jackman* teaches that the toxicity of pemetrexed would be reduced if administered together with folic acid without affecting the antitumor effect. *Jackman* taught unequivocally that, thanks to folic acid administration, not only could a higher dose of pemetrexed be administered, but also the side effects could be reduced (act. 35, margin nos. 15 - 16). Plaintiff sees a reference to this interpretation in paragraph [0039] of the patent in suit, where only the result was given that tumor suppression of 100% would also be achieved at a dose from 30 mg/kg with folic acid supplementation (act. 35, margin no. 19).

Assessment of an Inventive Step in Relation to "Antifolate Drugs in Cancer Therapy" ("*Jackman*", act. 1_28):

Jackman (act. 1_28) is a monograph on antifolates in cancer therapy. Chapter 8 deals with studies on the MTA antifolate LY231514 (= pemetrexed), while chapter 12 deals with studies on the GARFT inhibitors lometrexol and LY309887.

Chapter 8 contains the following passage in chapter 2.6 on page 191:

> *"However, if daily folic acid supplementation (15 mg/d/mouse, po) was given in conjunction with MTA, excellent antitumor dose-response (10 mg/kg to 1000 mg/kg, with antitumor activity ranging from 80 to 100 %) and no lethality was observed. (...) These data suggest that folate supplementation not only modulates the toxicity but also slightly enhances the antitumor response of MTA,"*

From this passage it can indeed be concluded that it is recommended to administer folic acid combined with pemetrexed.

The passage is followed immediately thereafter by Fig. 4 on page 192:

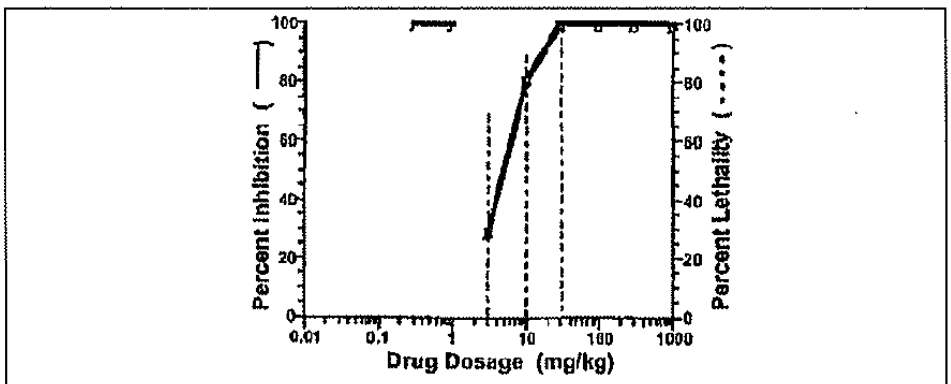


Fig. 4. Antitumor activity of MTA against L5178Y/TK⁻/HX⁻ lymphoma for mice on low folate diet (LFD) with no folate supplementation (J) and for mice on low folate diet that received 15 mg/kg/d daily folate supplementation (B); vertical dashed lines represent percent lethality in mice on low folate diet with no folate supplementation.

It is shown here that full inhibition (= antitumor effect) is already achieved with a lower dose (data at the top left) of pemetrexed without folic acid and that with folic acid administration this full inhibition is only achieved with a significantly increased dose of pemetrexed, at which high lethality can already be observed when administered without folic acid. In other words, Fig. 4 does not show an increase of the antitumor effect by folic acid, as mentioned in the first passage ("*slightly enhances the antitumor response*") but - on the contrary - a reduction.

It is difficult to judge how the person skilled in the art would have dealt with this situation of contradictory recommendations and which one he would have followed. However, he would not have decided in favor of supplementary administration of folic acid without any doubts. Even if he had nevertheless decided to administer folic acid, he would certainly have been cautious and would have continued to have reservations.

It is also clear that the skilled person, on the other hand, would also view the two documents concerning Phase I studies (act. 7_21, act. 7_22) as confirmation that the addition of folic acid would require higher doses of pemetrexed, but would also conclude from these that the addition of folic acid would reduce the toxicity of pemetrexed.

Due to Fig. 4, the argument of Defendant is conclusive that the person skilled in the art would have no motivation to supply folic acid to the patient and thus wuld be forced to massively increase the pemetrexed dose in order to achieve 100% inhibition, if he had already achieved 100% inhibition at a significantly lower dose but without folic acid. This view is in line with the decision of the Court of The Hague (act. 39_57, point 4.14).

It remains undisputed, however, that chapter 8 contains no reference to vitamin B12 or a pharmaceutical derivative thereof.

Regardless of whether or not the skilled person would administer folic acid with pemetrexed for the treatment of cancer, it remains to be determined whether he would have administered vitamin B12 (with or without folic acid) for the solution of the object underlying the patent.

The underlying object of the patent in suit is to reduce the toxic effects of pemetrexed without adversely affecting the therapeutic efficacy of the antifolate [0005]. The patent in suit solves this object by the use of vitamin B12 or a pharmaceutical derivative thereof, alone or in combination with folic acid.

As stated above, chapter 8 contains no reference to vitamin B12 or a pharmaceutical derivative thereof.

Chapter 12 of *Jackman*, on the other hand, contains a reference to vitamin B12 on page 270:

be unexpected, Furthermore, dietary supplementation with folic acid may "normalize" the dose response for achieving antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues having low folate requirements, without meeting the high folate demands of rapidly dividing tumor cells.

The biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B12 and B6. Thus, the status of all three vitamins in patients may significantly influence the severity of toxicity observed during chemotherapy. R. Allen and his col-

It should be emphasized that this passage from chapter 12 refers to other antifolates which, unlike pemetrexed, are not multi-target antifolates and that, if anything, this passage is to be understood as a non-verified recommendation due to its wording ("may").

Claims 1 - 11 of the patent in suit are directed to "mammals", which also include mice. Thus, the state of the art concerning mice and not humans is not to be regarded as irrelevant *per se*, but the person skilled in the art would consider it despite the differences and would examine its relevance more closely in a further step.

The fact that chapters 8 and 12 exist in the same monograph does not allow the conclusion that the person skilled in the art would necessarily have combined their disclosures. The chapters are written by different authors and therefore independent works. While they both deal with antifolates, lometrexol and LY309887 are GARFT inhibitors, whereas pemetrexed - in addition to GARFT - also inhibits TS and DHFR and is therefore a multi-target antifolate.

The fact that the structural similarities of lometrexol (and LY309887, for which, incidentally, no information on the structure has yet been provided) to pemetrexed disodium would have given rise to the combination of the disclosures of the two chapters cannot be regarded as certain simply because, as already mentioned in E. 23 in the *IBIS* discussion, it is very difficult to predict a pharmaceutical effect solely on the basis of a chemical formula. If in addition it is also known that lometrexol and pemetrexed have different mechanisms of action, this is to be expected even less.

The person skilled in the art therefore receives no motivation to combine the disclosure of chapter 8 with that of chapter 12 of *Jackman*.

Even if the person skilled in the art knows that vitamin B12 is required in the methylation cycle for the conversion of 5-methyltetrahydrofolate (5-MTHF) to tetrahydrofolate (THF) and that tetrahydrofolate (THF) plays an important role in the DNA cycle, so that those two cycles are linked to each other via

tetrahydrofolate, he also knows that vitamin B12 is a co-factor, and thus existing vitamin B12 is not consumed. Thus, in the presence of vitamin B12, the methylation cycle will not be completely blocked.

Thus, the skilled person will, also based on his common general knowledge, not see himself motivated to complement the teaching of *Jackman* in chapter 8 such that he would combine an administration of pemetrexed disodium with vitamin B12.

Consequently, the present claims 1 - 14 involve an inventive step in relation to *Jackman* (act. 1_28).

25. Inventive Step in Relation to the Document "An Overview of Folate Metabolism" ("*Calvert*", act. 1_7)

The Opposition Division of the European Patent Office maintained the patent in suit on the basis of *Calvert* (act. 1_7) as the closest state of the art. As a consequence, Plaintiff argues that there could be no inventive step if *Calvert* was used as a basis (act. 7, margin no. 179). *Calvert* disclosed a strong correlation between homocysteine levels in a patient's blood and the development of certain side effects during treatment with pemetrexed disodium. The reference "17" indicated thereby was D9 of the opposition (act. 7_10), which contains the further information that, according to the Opposition Division, allegedly no correlation between the pemetrexed side effects and the methylmalonic acid levels had been seen and would lead the person skilled in the art away from the supplementation with vitamin B12. Instead, the skilled person would supplement exclusively with folic acid (act. 1, margin no. 183).

Plaintiff tries to prove with several documents that this was not the case and that it was customary at the time of priority - and still is - to lower elevated homocysteine levels by adding folic acid and vitamin B12. In addition, the state of the art expressly encourages folic acid to always be administered together with vitamin B12, especially as a folic acid deficiency can also mask a vitamin B12 deficiency. Conversely, in the case of a vitamin B12 deficiency, the person skilled in the art would not only administer vitamin B12, but also folic acid, in order to ensure that homocysteine levels are completely lowered. It therefore did not matter whether a patient’s methylmalonic acid levels were elevated, since it always resulted in a combination of folic acid and vitamin B12 (act. 1, margin no. 186).

Accordingly, *Niyikiza* et al. (act. 1_19) did not state any methylmalonic acid levels either, but only the homocysteine levels were considered relevant. With this initial situation, a person skilled in the art would have had cause to lower homocysteine levels in any case by administering vitamin B12 and folic acid. On the basis of a single abstract (D9), which did not recognize the correlation, the Opposition Division had come to the conclusion that an inventive step existed (margin no. 188). This alleged non-correlation of pemetrexed side effects and methylmalonic acid levels of D9 (act. 7_10) had proved to be incorrect, which the same author of D9 confirmed in an article (act. 1_32) written later (act. 1, margin nos. 190, 192).

Furthermore, by analogy, the claims were not inventive starting from *Calvert* in combination with the common general knowledge, either (act. 1, margin no. 194).

Defendant submits that the Opposition Division had confirmed the legal validity of the patent in suit in a legally binding manner; the teaching of the patent in suit was novel and the combination therapy with vitamin B12 was not rendered obvious (act. 7, margin no. 257). Defendant criticizes that Plaintiff did not deal with D9 (act. 7_10) and rather relied on another publication of the same authors, i.e. act. 1_19. Plaintiff did not base its assertion on facts, but merely denied that there was no correlation between the toxicity effects caused by pemetrexed and the observed MMA levels (act. 7, margin no. 260).

With act. 1_32, Plaintiff relied on a post-published article by attempting to argue that lack of an inventive step could be established on the basis of conclusions drawn from a post-published document and the fact that it formulated a clinical hypothesis on the basis of information which was not publicly known at the time of priority. This hypothesis showed that Plaintiff relied on an ex post facto analysis and used hindsight to look at the technical problem (act. 7, margin no. 273). Furthermore, Defendant asserts that the new finding of act. 1_32 that the baseline vitamin B12 status measured by the MMA concentration was a predictor of toxicity risk had been decisive for the administration of vitamin B12 with pemetrexed. In addition, however, this preliminary information was known only to Defendant on the priority date of the patent in suit and further analyses were necessary to verify this clinical hypothesis (act. 7, margin no. 277).

Document D9 (act. 7_10) refuted Plaintiff's unfounded claim and showed that the MMA values had been analyzed and that no correlation had been found (act. 7, margin no. 261).

The reference to *Niyikiza* et al (act. 1_19) was not relevant. Niyikiza came to the same conclusion as act. 1_10, namely that, of the measured vitamin metabolites (homocysteine, cystathionine and MMA), only homocysteine showed correlations (but no causality) with toxicities. No such relationship was found for MMA levels. The person skilled in the art therefore received no indication that vitamin B12 had anything to do with the toxicities of pemetrexed treatment, let alone an incentive to administer vitamin B12 (act. 7, margin no. 264). This view had also been confirmed by the Opposition Division.

Moreover, it was completely fictitious and wrong that it was an established measure to "always" treat elevated homocysteine levels with folic acid and vitamin B12 and that this was regarded as "standard practice" in antifolate therapy. On the contrary, folates and classical antifolates used the same transport system and binding sites and thus elevated folate levels competed with antifolates and undermined their therapeutic and life-saving efficacy, such that the skilled person would not consider administering vitamin B12. This knowledge was supported by numerous literature sources, which taught away from the administration of vitamin B12 to cancer patients, since it was assumed that vitamin B12 accelerated tumor growth (act. 7, margin no. 268).

Defendant argues that the skilled person, based on observations from other medical fields, namely cardiovascular diseases where homocysteine is considered to be the cause, would not resort to the administration of vitamin B12. Toxicity was caused by the antifolate pemetrexed and homocysteine was regarded only as a marker, as shown in act. 7_10 and act. 1_19 (act. 7, margin no. 269).

Assessment of an Inventive Step in Relation to "An Overview of Folate Metabolism" ("*Calvert*", act. 1_7):

Calvert (act. 1_7) gives an overview of folate metabolism and describes the cancer fighting effects of pemetrexed (MTA) and its toxicity.

The object underlying the patent in suit is to reduce the toxic effects of pemetrexed without negatively affecting the therapeutic efficacy of the antifolate [0005]. The patent in suit solves this object by the use of vitamin B12 or a pharmaceutical derivative thereof, alone or in combination with folic acid.

It is undisputed that *Calvert* does not disclose either vitamin B12 or its methylmalonic acid marker.

Page 9 states the following information, which was heavily discussed:

> (Fig 8). The measurement of pretreatment plasma hornocysteine has proved to be a sensitive way of predicting the toxicity of MTA. [17]

The reference 17 mentioned in this passage corresponds to act. 7_10. Thus, the disclosure content of act. 7_10 is a key point in the discussion regarding the inventive step in relation to *Calvert*, especially with regard to the correlation between toxicity and methylmalonic acid levels. This question has already been discussed in detail in E. 22. The conclusion drawn there, which is also valid here, that act. 7_10 shows no correlation between toxicity and methylmalonic acid is in accordance with the decision of the Opposition Division (act. 7_36).

Plaintiff's attempt to prove with a post-published document (act. 1_32) that the alleged non-correlation of pemetrexed side-effects and methylmalonic acid values of act. 7_10 proved to be incorrect in retrospect, is without merit, since the content of act. 1_32 was simply not publicly available at the time of filing, apart from the fact that it cannot be ruled out that in principle any authors can change their opinion over time.

Therefore, act. 7_10 offers no basis for a correlation or for the relevance of methylmalonic acid levels and certainly no motivation for combining the feature missing in *Calvert*, vitamin B12, with pemetrexed disodium and thus to solve the problem described.

Thus, the present claims 1 - 14 also involve an inventive step in relation to *Calvert* (act. 1_7) as the closest state of the art.

26. Inadmissible Amendment

Plaintiff asserts an inadmissible amendment of claim 1. Plaintiff sees this inadmissible amendment in particular in the fact that the original claim 1 "*Method for administering...*" was changed to a Swiss type claim, the class "*antifolate*" was replaced by "*pemetrexed disodium*" and the compound class "*methylmalonic acid binding agent*" was replaced by a selection of specific compounds (act. 1, margin no. 171).

There is however no support for this selection of specific features (compounds) from several lists in the patent application as originally filed. In particular, the combination of features now contained in claim 1 of the patent in suit was not disclosed in an individualized form, which constituted a requirement for the admissibility of the amendment, according to the relevant case law of the Boards of Appeal of the European Patent Office (act. 1, margin no. 174).

Defendant objects to the existence of an inadmissible amendment. In particular, Defendant points out that, on the one hand, the change to the Swiss type claim format had been made correctly in order to meet the requirements of the European Patent Convention (act. 7, margin no. 252). On the other hand, the restricted features mentioned had been contained in a combination of the original claim 3 (reformulated as a "Swiss type" claim) with the dependent claims 7 and 9 (act. 7, margin no. 254). Thus, all of the features mentioned resulted directly and unambiguously from the description and claims of the version as originally filed.

In particular, there was no selection from any lists. T 727/00 concerned a combination of features selected from a list of 23 elements and a list of 6 elements (act. 7, margin no. 256).

Assessment of the Inadmissible Amendment:

The restricted features "pemetrexed disodium", "inhibition of tumor growth" and "vitamin B12" can be clearly identified in the original claims 3, 7 and 9 in combination with the disclosure on page 7, lines 5 - 7 (Alimta). Due to the interdependencies of the dependent claims, the individual combination of these elements is to be assessed as established. The reformulation of the original claim wording into a "Swiss type" claim does not change this assessment.

Thus, there is no "selection from lists" as a result of the restriction made and an inadmissible amendment does not exist.

27. Conclusion

In summary, the granted claims 1 - 14 are novel in relation to *Worzalla* (act. 1_12), none of Plaintiff's attacks regarding lack of an inventive step is convincing, and the patent in suit has not been amended inadmissibly. Accordingly, the action for revocation must be dismissed.

Costs and Compensation

28.
In accordance with the outcome, Plaintiff is liable for costs and compensation (Art. 106 para. 1 of the Swiss Code of Civil Procedure (ZPO)). Based on an amount in dispute of CHF 1.5 million (act. 1, margin no. 6, act. 7, margin no. 1), the court fee is to be set at CHF 80,000, is to be borne by Plaintiff and to be offset against Plaintiff’s advance payment on costs (Art. 1 of the Regulations on Litigation Costs at the Federal Patent Court (*Reglement über die Prozesskosten beim Bundespatentgericht - KR-PatGer*), Art. 111 para. 1 of the Swiss Code of Civil Procedure). The interpreter costs in the amount of CHF 2,977 (cf. act. 62, 63) were caused by Defendant and are to be borne by Defendant.

29.
The compensation for the professional legal representation is to be set at CHF 50,000 since the costs of professional legal representation were significantly lower than the patent attorney costs (cf. Art. 3 - 5 of the Regulations on Litigation Costs at the Federal Patent Court (LR-PatGer)). Defendant claims CHF 77,400 for the patent attorney costs (act. 60), which is acknowledged by Plaintiff (act. 61, p. 17).

The Federal Patent Court finds:

1. The action is dismissed.
2. The court fee is set at CHF 80,000.

   The other costs amount to CHF 2,977 (interpreting costs).

3. CHF 80,000 (court fee) of the costs will be borne by Plaintiff and offset against its advance on costs. The further costs of CHF 2,977 (interpreter costs) will be borne by Defendant.

4. Plaintiff is obligated to pay to Defendant a compensation for attorneys' and parties' expenses of CHF 127,400.

5. Written notification to the parties, each accompanied by act. 61, to Defendant accompanied by invoice no. 1185001328, and to the Swiss Federal Institute of Intellectual Property (IGE) (once legally valid), each against acknowledgement of receipt.

Information on the Possibilities of Contestation and Appeal:

An appeal in civil cases may be lodged against this decision with the Federal Court, 1000 Lausanne 14, Switzerland, within **30 days** of its opening (Art. 72 et seq., 90 et seq. and 100 of the Swiss Federal Court Act of 17 June 2005 [Bundesgerichtsgesetz - BGG, SR 173.110]). The legal document shall be drafted in an official language and shall contain the request, its justification with specification of the evidence and the signature. The contested decision and the evidence shall be attached, as far as they are in the possession of the appealing party (cf. Art. 42 of the Swiss Federal Court Act).

St. Gallen, 15 October 2019

In the name of the Federal Patent Court

Instructing Judge	First Law Clerk
	
Dr. iur. Daniel M. Alder	lic. iur. Susanne Anderhalden

Delivery: 2 1 OCT. 2019