judgment

DISTRICT COURT OF THE HAGUE
Commerce team

case number/cause-list number: C/09/533354 / HA ZA 17-581

Judgment of 16 January 2019

in the case of

the legal entity under foreign law
SANDOZ INTERNATIONAL GMBH,
at Holzkirchen, Germany,
claimant,
counsel: D.F. de Lange in Amsterdam,

versus

the legal entity under foreign law
ELI LILLY AND COMPANY,
at Indianapolis, Indiana, United States of America,
defendant,
counsel: J.A. Dullaart in Naaldwijk.

The parties will hereinafter be referred to as Sandoz and Lilly.

The case was handled for Sandoz by the aforementioned lawyer, together with mr. A.D. de Leeuw and mr. B.J.M. van der Maazen, lawyers in Amsterdam, and for Lilly by mr. L. Oosting, mr. K.A.J. Bisschop and mr. ing. H.J. Ridderinkhof, lawyers in Amsterdam.

1. The proceedings

1.1. The course of the proceedings is apparent from:
- the decision of the preliminary relief judge of this District Court of 15 December 2016 in which leave was granted to issue a summons according to the scheme for accelerated proceedings on the merits in patent cases,
- the summons of 5 January 2017,
- the document commenting on exhibits, also Sandoz' opinion of the preliminary relief proceedings judgment of 14 June 2017, with exhibits EP01 to EP50,
- the statement of defence of 23 August 2017, with exhibits GP01 to GP14,
- the document commenting on further exhibits of Sandoz of 29 November 2017, with exhibits EP51 to EP54,
- the document commenting on additional exhibits of Lilly of 29 November 2017, with exhibits GP15 to GP18,

- the document commenting on responding exhibits of Sandoz of 5 January 2018, with exhibit EP55,
- the document commenting on responding exhibits of Lilly of 5 January 2018, with exhibits GP19 to GP29,
- the email of 12 January 2018 from Lilly with a cost statement and breakdown;
- the email of 25 January 2018 from mr. De Leeuw in which he communicates on behalf of both parties that an agreement has been reached on the reasonable and proportionate legal costs in the amount of €300,000, which the losing party should be ordered to pay;
- the oral arguments of 26 January 2018 and written pleadings used by the parties in them, where in Sandoz' written pleadings marginal numbers 13, 15 (first bullet point from "To the OD decision"), 36 under 3., 72 (from "Note"), 73, 75, 76 opening words and under 1. and 4. as well as footnote 7 have been crossed out because they were not put forward. In the written pleadings of Lilly, marginal numbers 2.6, second quote, 3.1-3.3 and 4.25-4.30 have been crossed out for the same reason.

1.2. Finally, judgment was scheduled for today.

2. The facts

2.1. Sandoz is part of the Novartis group and is active in the field of development, production and distribution of generic medicines.

2.2. Lilly is part of the Eli Lilly group, which is active in the field of research, development and marketing of new medicines.

2.3. Lilly markets the medicine Alimta®, which - in short - is indicated for the treatment of certain lung cancers. Alimta® contains the active ingredient pemetrexed disodium. Pemetrexed is an antifolate that was also referred to as LY231514 or MTA in the prior art.

2.4. Lilly is the holder of European patent 1 313 508 B1 (hereinafter: EP 508), entitled '*Combination containing an antifolate and methylmalonic acid lowering agent'*. The claims refer to the use of a combined preparation containing the active ingredient pemetrexed disodium. EP 508 was granted on 18 April 2007 on an application of 15 June 2001 with an appeal to priority of US 215310 P of 30 June 2000, US 235859 P of 27 September 2000, and US 284448 P of 18 April 2001[1]. The antifolate pemetrexed was initially protected by EP 0 432 677 (hereinafter: EP 677). EP 677 is the basic patent for Supplementary Protection Certificate 300181 for '*pemetrexed, if desired, in the form of a pharmaceutical acceptable salt'* (hereinafter: the SPC). The SPC was in force until 9 December 2015.

[1] Where reference is made in the following to the priority date, the first priority date of 30 June 2000 is meant.

2.5. EP 508 contains two independent claims (1 and 12) and the claims dependent on them (2 to 11 and 13 to 14) that in the original English language read as follows:

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.

2. Use according to claim 1 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, and a folic binding protein binding agent selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-forinyl-5,6,7,8-tetrahydrofohc acid or a physiologically available salt or ester thereof.

3. Use according to claim 2 wherein the folic binding protein binding agent is folic acid.

4. Use according to any one of claims 1 to 3 wherein the vitamin B12 or pharmaceutical derivative thereof is vitamin B12, cobalamin or chlorocobalamin.

5. Use according to any one of claims 1 to 3 wherein the vitamin B12 or pharmaceutical derivative thereof is selected from vitamin B12 or hydroxocobalamin.

6. Use according to any one of claims 1 to 5 wherein the medicament, the vitamin B12 or pharmaceutical derivative thereof and optionally the folic binding protein binding agent are to be administered simultaneously, separately or sequentially.

7. Use according to any one of claims 1 to 6 wherein the medicament is to be administered after administration of the vitamin B12 or pharmaceutical derivative thereof.

8. Use according to any one of claims 1 to 7 wherein the medicament is to be administered after the folic binding protein binding agent.

9. Use according to any one of claims 2 to 8 wherein the medicament is to be administered after pretreatment with the vitamin B12 or pharmaceutical derivative thereof followed by folic acid.

10. Use according to any one of claims 1 to 9 wherein vitamin B12 or pharmaceutical derivative thereof is to be administered as an intramuscular injection.

11. Use according to any one of claims 2 to 10 wherein the folic binding protein binding agent is to be administered orally as a tablet.

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.

13. A product according to claim 12 wherein the vitamin B12 or pharmaceutical derivative thereof is vitamin B12, co-balamin or chlorocobalamin and, if present, the folic binding protein binding agent is folic acid.

14. A product according to claim 12 wherein the vitamin B12 or pharmaceutical derivative thereof is vitamin B12 or hydroxocobalamin and, if present, the folic binding protein binding agent is folic acid.

2.6. In the Dutch translation the claims of EP 508 read as follows.

1. Toepassing van pemetrexed dinatrium bij het bereiden van een geneesmiddel voor toepassing bij combinatietherapie voor het remmen van tumorgroei bij zoogdieren, waarbij het geneesmiddel dient te worden toegediend in combinatie met vitamine B12 of een farmaceutisch derivaat daarvan, waarbij het farmaceutisch derivaat van vitamine B12 hydroxocobalamine, cyaan-10-chloorcobalamine, aquocobalamine perchloraat, aquo-10-chloorcobalamine perchloraat, azidocobalamine, chloorcobalamine of cobalamine is.

2. Toepassing volgens conclusie 1, waarbij het geneesmiddel dient te worden toegediend in combinatie met vitamine B12 of een farmaceutisch derivaat daarvan, waarbij het farmaceutisch derivaat van vitamine B12 hydroxocobalamine, cyaan-10-chloorcobalamine, aquocobalamine perchloraat, aquo-10-chloorcobalamine perchloraat, azidocobalamine, chloorcobalamine of cobalamine is, en een foliumbindend eiwit bindend middel gekozen uit foliumzuur, (6R)-5-methyl-5,6,7,8-tetrahydrofoliumzuur en (6R)-5-formyl-5,6,7,8-tetrahydrofoliumzuur of een fysiologisch aanvaardbaar zout of ester daarvan.

3. Toepassing volgens conclusie 2, waarbij het foliumbindende eiwitbindende middel foliumzuur is.

4. Toepassing volgens een of meer van de conclusies 1-3, waarbij het vitamine B12 of het farmaceutische derivaat daarvan vitamine B12, cobalamine of chloorcobalamine is.

5. Toepassing volgens een of meer van de conclusies 1-3, waarbij het vitamine B12 of het farmaceutische derivaat daarvan is gekozen uit vitamine B12 of hydroxocobalamine.

6. Toepassing volgens een of meer van de conclusies 1-5, waarbij het geneesmiddel, het vitamine B12 of het farmaceutische derivaat daarvan en eventueel het foliumbindende eiwitbindende middel tegelijkertijd, afzonderlijk of achtereenvolgens dienen te worden toegediend.

7. Toepassing volgens een of meer van de conclusies 1-6, waarbij het geneesmiddel dient te worden toegediend na toediening van het vitamine B12 of het farmaceutische derivaat daarvan.

8. Toepassing volgens een of meer van de conclusies 1-7, waarbij het geneesmiddel na het foliumbindende eiwitbindende middel dient te worden toegediend.

9. Toepassing volgens een of meer van de conclusies 2-8, waarbij het geneesmiddel dient te worden toegediend na voorbehandeling met het vitamine B12 of het farmaceutische derivaat daarvan gevolgd door foliumzuur.

10. Toepassing volgens een of meer van de conclusies 1-9, waarbij het vitamine B12 of het farmaceutische derivaat daarvan als een intramusculaire inspuiting dient te worden toegediend.

11. Toepassing volgens een of meer van de conclusies 2-10, waarbij het foliumbindend eiwitbindend middel als een tablet oraal dient te worden toegediend.

12. Product dat pemetrexed dinatrium, vitamine B12 of een farmaceutisch derivaat daarvan, waarbij het farmaceutisch derivaat van vitamine B12 hydroxocobalamine, cyaan-10-chloorcobalamine, aquocobalamine perchloraat, aquo-10-chloorcobalamine perchloraat, azidocobalamine, chloorcobalamine of cobalamine is, en eventueel een foliumbindend eiwitbindend middel gekozen uit de groep bestaande uit foliumzuur, (6R)-5-methyl-5,6,7,8-tetrahydrofoliumzuur en (6R)-5-formyl-5,6,7,8-tetrahydrofoliumzuur, of een fysiologisch aanvaardbaar zout of ester daarvan, als een gecombineerd preparaat voor gelijktijdige, afzonderlijk of achtereenvolgend gebruik bij remmen van tumorgroei, bevat.

13. Product volgens conclusie 12, waarbij het vitamine B12 of het farmaceutische derivaat daarvan vitamine B12, cobalamine of chloorcobalamine is en, indien aanwezig, het foliumbindende eiwitbindende middel foliumzuur is.

14. Product volgens conclusie 12, waarbij het vitamine B12 of farmaceutisch derivaat daarvan vitamine B12 of hydroxocobalamine is en, indien aanwezig, het foliumbindend eiwitbindend middel foliumzuur is.

2.7. The description of the patent - as far as important here - includes the following:

[0001] Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (Antifolate, pg 197.)
[0002] Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer. (...) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (...) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex®. An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway.
For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, IN) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.
[0003] A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally antifolates as a class are associated with sporadic severe mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (...)
[0004] Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (...). The role of folic acid in modulating the toxicity and efficacy of the multitargeted antifolate LY 231514 (pemetrexed) was discussed in Worzalla *et al.* (Anticancer Research 18: 3235-3240 (1998) Worzalla JF, Chuan S and Schultz RM). EP-A-0546870 relates to nutrient compositions which are intended to prevent and cure infectious diseases and which are intended to be administered to patients being administered with anticancer drugs to prevent and treat infectious diseases due to immunosuppression induced by the anticancer drug therapy. The compositions of EP-A-0546870 are characterized in that they comprise a certain amount of retinoid compound(s) such as vitamin A which is indicated as being responsible for the immunoreactivity. Effects of vitamin B12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations (Lancet 1995; 346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.
[0005] Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic 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. The present invention thus generally relates to a use in the manufacture of a medicament for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent as vitamin B12. We have discovered that increased levels of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin B12, reduces mortality and nonhematologic events, such as skin

rashes and fatigue events previously associated with the antifolate drugs. Thus, the present invention generally relates to a use in the manufacture of a medicament for reducing the toxicity associated with the administration of an antifolate to a mammal by administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent as vitamin B12.
[0006] Additionally, we have discovered that the combination of a methylmalonic acid lowering agent as vitamin B12 and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

2.8. Various proceedings have been brought regarding EP 508 and non-European patents related to EP 508, some of which are mentioned here below.

2.8.1. Teva Pharmaceuticals Industries Ltd., has filed opposition against the grant of EP 508 including an appeal to lack of inventive step. The Opposition Division of the European Patent Office dismissed that appeal and by decision of 18 November 2010, elaborated on in the grounds of the decision of 27 December 2010, left the patent unchanged. The appeal made against it has been withdrawn.

2.8.2. In Germany, by decision of 20 May 2016 the Landgericht Munich upheld an earlier ex parte decision given, which imposed an injunction on the company Hexal AG (which like Sandoz belongs to the Novartis group) in respect of a combination of generic pemetrexed, vitamin B12 and folic acid. EP 508 was therefore considered valid for the time being. Hexal AG brought invalidity proceedings at the German Bundespatentgericht with regard to the German part of EP 508, of which the oral handling at the time of the oral pleadings in this case was expected in July 2018. The District Court knows ex officio that the Bundespatentgericht nullified the German part of EP 508 by decision of 17 July 2018.[2]

2.8.3. In the United States, Lilly brought proceedings against Teva Parenteral Medicines, Inc and Teva Pharmaceuticals USA, Inc. amongst others. By judgment of 31 March 2014, the District Court for the Southern District of Indiana found the US patent 7,772,309 parallel to EP 508 valid and assumed infringement. This judgment was upheld on appeal by the United States Court of Appeals for the Federal Circuit by decision of 12 January 2017. The United States Patent and Trademark Office also found this patent valid by decisions of 5 October 2017, in proceedings between Sandoz and Lilly.

2.8.4. In the Netherlands, Lilly brought preliminary relief proceedings at this District Court against a sister company of Sandoz, Sandoz B.V., after a generic version of pemetrexed was included in its name in the G-standard of Z-index for February 2017, published on 17 January 2017, for which the medication leaflet prescribed administration in combination with folic acid and vitamin B12. By judgment of 1 March 2017, the preliminary relief judge imposed an injunction on Sandoz B.V. in respect of EP 508.

2.8.5. In addition, Lilly sued Teva Netherlands B.V. (hereinafter: Teva) and Fresenius Kabi Nederland B.V. (hereinafter: Fresenius) in preliminary relief proceedings for the marketing of a generic drug with the active substance pemetrexed diacid (in Dutch:

[2] ECLI:DE:BPatG:2018:170718U3Ni23.16EP.0

pemetrexed dizuur), which drug is prescribed in combination with a vitamin supplement that consists of folic acid administered orally, and vitamin B12 administered by intramuscular injection. In judgments of 24 October 2017, the preliminary relief judge of this District Court imposed an injunction on Teva and Fresenius. The aforementioned judgments were upheld by the Appeals Court of The Hague in rulings of 8 May 2018. Fresenius brought appeal at the Supreme Court.

2.8.6. Proceedings on the merits between Lilly and Fresenius on infringement of EP 508 are pending before this District Court. Oral arguments in that case were held on 11 July 2018. The judgment in that case is expected soon.

2.9. The following publications belonged to the prior art on the priority date of EP 508.

2.9.1. The following abstract by J.F. Worzalla e.a. was published in the publication '*Scientific Proceedings, 88th Annual Meeting of the American Association for Cancer Research'* (Volume 38, March 1997, p. 478) (hereinafter: the Worzalla abstract):

#3198 Effects of folic acid on toxicity and antitumor activity of LY231514 multi-targeted antifolate (MTA). Worzalla, J.F., Self, T.D., Theobald, K.S., Schultz, R.M., Mendelsohn, L.G., and Shih, C. *Lilly Research Labs, Indianapolis, IN 46285*

Supplemental folic acid is used clinically in cancer and rheumatoid arthritis to ameliorate the toxicities of antifolate agents including inhibitors of dihydrofolate reductase, glycinamide ribonucleotide formyltransferase and thymidylate synthase. The pentaglutamylated form of MTA is a potent inhibitor of these three enzymes. Therefore, the effects of folic acid on the activities of MTA were studied. *In vitro*, using a variety of human carcinoma and leukemia cell lines grown in low folate media, folic acid was 100- to 1000-fold less active than folinic acid at protecting the cells from MTA-induced cytotoxicity; folic acid >1 μM was required to exert protection. *In vivo*, the lethality of MTA for mice maintained on standard diet (SD) or low folate diet (LFD) was determined; the LD_{50} in several strains of mice occurred at 30 to 250-fold lower concentrations of MTA for mice on LFD as compared to SD. For mice on LFD, MTA at 0.3 and 1 mg/kg (qdx10, i.p.) produced 100% inhibition of L5178Y/TK-/Hx- lymphoma; significant lethality was seen at 3 mg/kg and higher doses. For mice on SD, MTA produced >95% inhibition of tumor growth at 30 to 300 mg/kg, but all mice died at 800 mg/kg. For mice on LFD supplemented p.o. with 15 mg/kg daily folic acid, 100% tumor inhibition was seen from 30 to 1000 mg/kg with no lethality. Thus, addition of oral folic acid did not reduce antitumor activity of MTA, but did lessen toxicity.

2.9.2. The article '*Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514*' by J.F. Worzalla e.a. (hereinafter: Worzalla or de Worzalla study) appeared in the journal Anticancer Research (1998, 18: 3235-3240). It includes:

Abstract. *We studied the effects of folic acid on modulating the toxicity and antitumor efficacy of LY231514. Using several human tumor cell lines adapted to growth in low folate medium, folic acid was shown to be 100- to 1000-fold less active than folinic acid at protecting cells from LY231514-induced cytotoxicity. The lethality of LY231514 was compared in mice maintained on standard diet or low folate diet. The LD50 occurred at 60- and 250-fold lower doses of LY231514 in DBA/2 and CDI nu/nu mice, respectively, maintained on low folate diet compared to standard diet. The L5178Y/TK-/HX-murine lymphoma was much more sensitive to the antitumor action of LY231514 compared to wild type L5178Y-S tumors. For mice on low folate diet, LY231514 at 0.3 and 1 mg/kg (qd x 10, i.p.) produced 100% inhibition of L5178Y/TK-/HX-lymphoma growth, and significant lethality*

occurred at ≥ 3 mg/kg. For mice on standard diet, LY231514 produced > 95% inhibition of tumor growth at 30 to 300 mg/kg, but all mice died at 800 mg/kg. Folic acid supplementation was demonstrated to preserve the antitumor activity of LY231514 while reducing toxicity. The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity.

(…)
Several animal studies have indicated that folic acid supplementation in combination with antifolate cancer therapy can prevent delayed toxicity and enhance the therapeutic potential of the GARFT inhibitor lometrexol and the TS inhibitor 1843U89. Unexpected delayed cumulative toxicity was observed in phase I studies with lometrexol, including thrombocytopenia, anemia, and mucositis. Additional clinical studies demonstrated the protective effects of folic acid against lometrexol toxicity in humans. Morgan and coworkers concluded that a daily supplement of 1 mg of folic acid during low-dose methotrexate therapy in patients with rheumatoid arthritis was useful in lessening toxicity without altering efficacy. In the present communication, we investigated the effects of folic acid on the antitumor activity and lethality of LY231514 in mice.

Materials and Methods

(…)

Cell lines. (…) The L5178Y/TK-/HX-murine lymphoma cell line was obtained from Eli Lilly Department of Genetic Toxicology (Greenfield, IN, USA).The tumor is a double mutant, deficient in thymidine kinase and hypoxanthine phosphoribosyl transferase.

(…)

Mice. Female CD I nu/nu mice were purchased from Charles River Laboratories (Wilmington, MA, USA). Female DBA/2 mice were purchased from Taconic (Germantown, NY, USA). Mice weighed 20 to 25 grams at the beginning of the studies. Mice were housed in temperature and humidity controlled rooms. Mice were fed either standard laboratory rodent chow (Purina Chow #5001) or folic acid-deficient diet containing 1% succinylsulfathiazole (Purina Chow #5831C-2); both diets were purchased from Ralston Purina Co. (St. Louis, MO, USA). The average content of folates from natural sources in both diets was found to be 0.03 ppm, whereas the standard diet was analyzed to contain 7.3 ppm of added folic acid. It was estimated that mice on a standard diet ingested 1 to 2 mg/kg/day of folates, while mice on a low folate diet ingested 0.001 to 0.008 mg/kg/day. In some studies, mice received solubilized folic acid once a day by oral gavage. Food and water were provided ad libitum.

(…)

Results

(…)

Role of folic acid in the antitumor activity of LY231514 against the L5178Y murine lymphoma. (…) The exquisite sensitivity of the L5178Y/TK-/HX- tumor model to LY231514 treatment allowed us to evaluate the effect of low folate diet on the therapeutic activity of this compound. For mice on LFD, LY231514 at 0.3 and 1.0 mg/kg/day (i.p. qd x10) produced 100% inhibition of tumor growth for tumors measured one day after the completion of a single course of drug treatment (Figure 2). As noted in Figure 1, higher drug levels yielded unacceptable toxicity. For mice on LFD that received a folate supplement of 15 mg/kg/day via oral gavage, significant inhibition of tumor growth was noted over a broad dose range (10- 1000 mg/kg/dose). Moreover, 100% inhibition of tumor growth was observed at 30 to 1000 mg/kg/dose without any lethality. This antitumor dose response (with folate supplementation) was virtually identical to that observed for mice receiving standard diet. However, the lethality was signicantly [sic] greater for the mice on standard diet (lethality at 400 and 800 mg/kg/day of 10% and 100%, respectively). Mice on standard diet received approximately one-tenth of the amount of daily folic acid as the mice on LFD with 15 mg/kg/day supplemental folic acid.

Discussion

The poor predictive value of mouse models for antifolate toxicity may be partially due to the fact that standard laboratory mouse diets contain high levels of folic acid.

(…)

LY231514 produced potent antitumor activity against the L5178Y/TK-HX- lymphoma at 100-fold lower dose levels (0.3 and 1 mg/kg/day, Figure 2) in LFD mice relative to 30 and 100 mg/kg (Table II) in mice on standard diet. It is interesting to note that the LD_{50} was reduced 3000-fold for lometrexol in LFD animals, and antitumor activity could not be demonstrated even at low dose levels. In contrast, the shift in both LD_{50} and antitumor activity for mice on LFD compared to standard diet were of a similar magnitude (approximately 100-fold) for LY231514. However, LFD animals with high levels of folate supplementation demonstrated decreased lethality to LY231514 compared to conventional diet animals, suggesting that folate intake can be manipulated to achieve greater therapeutic effects. Oral folic acid dramatically decreased the toxicity of LY231514 and preserved antitumor activity (albeit at higher dose levels) in these mice (Figure 2).

Table II and figures 1 and 2 to which reference is made in the above passages are shown below:

Table II. *LY231514 antitumor activity against L5178Y/S wild type and L5178Y/TK-/HX-lymphoma.*

	Tumor Dose[a] (mg/kg)	% Tumor Inh.[b]	# Tumor-free/total day 10[c]	day 100
L5178Y/S				
	10	0	0/10	-
	30	8	0/10	-
	100	68	0/10	-
L5178Y/TK-/HX-				
	10	90	0/7	0/7
	30	100	5/7	6/7
	100	100	7/7	5/7

[a]LY231514 was administered i.p. on a qd x 10 schedule.
[b]Tumors were measured on the day following the last drug treatment.
[c]Days represent the number of days since therapy was initiated.

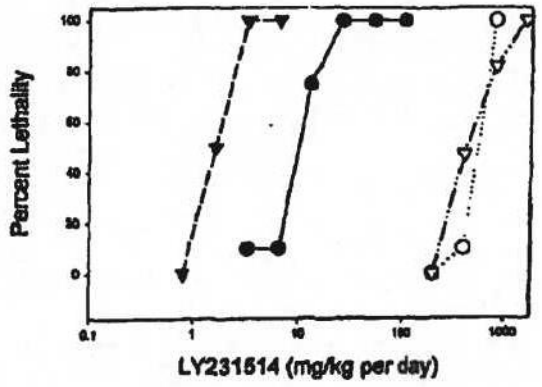

Figure 1. The toxicity of LY231514 in mice is increased by a folate-deficient diet. DBA/2 and CDI nu/nu mice were fed either a standard laboratory diet (○ and ▽, respectively) or a folate-deficient diet for 2 weeks prior to the first dose of LY231514 (● and ▼, respectively) and for the duration of the study. Groups of mice (> 10 animals/group) on each diet were given 10 daily doses of LY231514 i.p. at the indicated doses. The data present the percent lethality within 3 weeks after the last dose of LY231514.

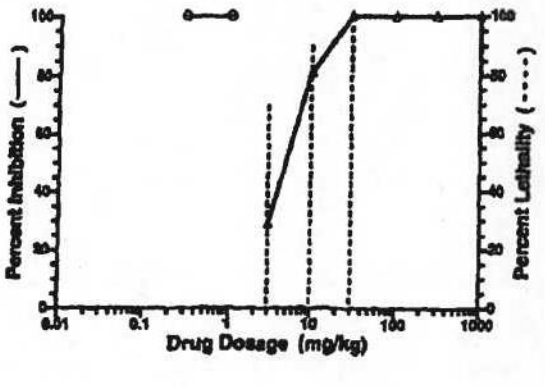

Figure 2. Antitumor activity of LY231514 therapy (i.p., qd ×10) against L5178Y/TK- /HX- lymphoma for mice on low folate diet with no folate supplementation (○) and for mice on low folate diet that received 15 mg/kg/day daily folate supplementation (△). Vertical dashed lines represent percent lethality in mice on low folate diet with no folate supplementation. No lethality was observed in mice that received folate supplementation.

2.9.3. The abstract here below by L. Hammond e.a. (hereinafter: Hammond I)[3]: was published by the *American Society of Clinical Oncology* (ASCO).

A PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE MULTITARGETED ANTIFOL (MTA) LY231514 WITH FOLIC ACID (Meeting abstract).

Sub-category: Other
Category: Clinical Pharmacology
Meeting: 1998 ASCO Annual Meeting

Abstract No: 866

Author(s): L Hammond, M Villalona-Calero, SG Eckhardt, R Drengler, C Aylesworth, T Johnson, M Hidalgo, G Rodriguez, S Diab, P Monroe, D Thornton, Hoff D Vo, E Rowinsky

Abstract: MTA (LY 231514) is a new antifol that inhibits multiple folate-dependent enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. Initial phase I trials demonstrated major antitumor responses when MTA was given as a 10 min I.V. infusion, however, myelosuppression precluded dose escalation above 500-600 mg/m2. Since preclinical studies indicated that folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. Thus far, 21 pts with solid cancers have received 55 courses at the following dose levels: 600, 700, and 800 mg/m2. Drug-related toxicities have included neutropenia, anemia, and thrombocytopenia, which have been more severe in heavily-pretreated pts. Other toxicities (grade 1-2) include rash, somnolence, fatigue, leg edema, and diminished renal function manifested by a decrease in creatinine clearance. One pt taking a non-steroidal anti-inflammatory agent experienced severe toxicities at the 800 mg/m2 dose, which resolved after administration of leucovorin and thymidine. One partial response in a pt with metastatic colon cancer has been observed. PK and vitamin (folic acid) metabolite profiles were done during cycles 1 and 3 at 600 to 800 mg/m2. To date, serum folic acid levels do not appear to be related to toxicity, but homocysteine was significantly elevated in the pt with severe toxicities at the 800 mg/m2 dose. Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m2 and accrual continues at 700 and 900 mg/m2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation.

2.9.4. The journal '*Annals of Oncology'* (Supplement 4 to Volume 9, 1998, p. 129) included the following publication by L. Hammond e.a. (hereinafter: Hammond II):

[3] Emphasis not added by the District Court

620P **A phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)**

L. Hammond[1], M. Villalona-Calero[1], S.G. Eckhardt[1], L. Siu[1], M. Hidalgo[1], D. Thornton[2], J. Walling[2], S. Baker, C. Coltman[1], D. Von Hoff[1], E. Rowinsky[1]. [1]*Cancer Therapy and Research Center, San Antonio, TX, and* [2]*Eli Lilly, Indianapolis, IN, USA*

Introduction: MTA, a new antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, demonstrated notable broad antitumour activity when infused 10 min i.v. every 21 days. Myelosuppression precluded dose escalation above 500–600 mg/m^2. As preclinical evaluations indicate that FA supplementation increases the therapeutic index of MTA, this study was initiated to determine if FA supplementation permits significant dose-escalation above the recommended phase II dose of MTA alone. Vitamin metabolites were measured to determine their value as potential prognostic markers with this combination.

Methods: So far, 33 minimally- and heavily-pretreated pts received 90 courses of FA (5 mg/day) for 5 days starting 2 days before MTA at 600, 700, 800 925 mg/m^2. Vitamin metabolites were evaluated during cycles 1 and 2 as potential determinants of principal toxicities and effects.

Results: Principal drug-related toxicities include neutropenia, anaemia and thrombocytopenia, which were more severe in heavily-pretreated pts. Other toxicities (grade (G) 1–2) include rash, somnolence, fatigue, leg oedema, and a decrease in creatinine clearance (CrCl). Severe toxicities in 2 pts, 1 who had taken a non steroidal anti-inflammatory agent and 1 with severe hypoalbuminaemia, resolved after administration of leucovorin and thymidine. Preliminary vitamin metabolites in 26 pts reveal: 2 and 3 of 11 pts with homocysteine ≥ 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 15 pts with homocysteine < 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 9 pts with elevated cystathionine levels (cystathionine upper limit of normal 342 nM/L) had G2 somnolence and G1–2 fatigue, respectively; 1 and 10 of 16 pts with normal cystathionine levels had G2 somnolence and G1–2 fatigue, respectively; 1 of 4 pts with elevated methylmalonic acid (methylmalonic acid upper limit of normal 271 nM/L) had G2 fatigue while 12 of 22 pts with normal levels had G1–2 fatigue. 7 of 15 pts with elevated homocysteine, cystathionine, or methylmalonic acid levels had a significant decrease in CrCl. Based on information from these 15 pts, addition of FA may reduce the usefulness of vitamin metabolites as predictors of toxicity.

Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity. Heavily- and minimally-pretreated pts tolerate MTA at 700 and 925 mg/m^2 and accrual continues at 800 and 925 mg/m^2, respectively.

2.9.5. The book '*Antifolate Drugs in Cancer Therapy'* (1999, Humana Press, Totowa, New Jersey) by A.L. Jackman (ed.) (hereinafter: Jackman), contains a contribution in chapter 8 by C. Shih and D.E. Thornton, entitled '*Preclinical Pharmacology Studies and the Clinical Development of a Novel Multitargeted Antifolate, MTA (LY231514)*' which includes the following (page 190 and 191):

2.6. The in Vivo Antitumor Effects and the Role of Folic Acid in Modulating the Efficacy and Toxicity of MTA

MTA was found to be highly active against the L5178Y/TK-/HX-lymphoma in mice *(35)*. An excellent therapeutic index was seen, along with antitumor activity in this thymidine kinase-deficient murine model, a result that is consistent with TS inhibition being the primary mode of action of MTA. Good antitumor activity was also observed for MTA in other human tumor xenografts that expressed normal level of thymidine kinase,

including VRC5 (colon, 80% growth inhibition) and GC3 (colon, 94% growth inhibition), BXPC3 (pancreas), LX-1 (lung), and MX-1 (breast) xenografts.
To evaluate the importance of dietary folate in modulating the toxicity of MTA, LD_{50} values were determined in mice maintained on standard diet (SD) or on a special low-folate diet (LFD) (*35*). MTA was administered ip daily for 10 d. It is estimated that mice on LFD consumed an average of approx 0.003 mg/kg/d of folic acid vs 0.75-1.5 mg/kg/d for mice on SD. Thus mice on SD had a daily intake of approx 250-500 times more folic acid than mice on LFD. MTA was more toxic to several different strains of mice maintained on LFD, with the LD_{50} values being 30- to 250-fold lower than mice maintained on SD. A similar effect had been observed for antipurine antifolates such as lometrexol. The MTD of lometrexol on LFD was 1000- to 5000-fold lower than in mice maintained on SD. DHFR inhibitors such as methotrexate had a similar effect but to a lesser extent (50- to 100-fold, J.F. Worzalla, unpublished observation). The therapeutic index of MTA against the L5178Y/TK-/HX- tumor was greatly diminished when the mice were put on a LFD (2 wk) with no folate supplementation. Good antitumor activity was observed at 0.3 mg/kg and 1.0 mg/kg (ip daily x 10) doses only, and significant toxicity was observed for MTA at higher doses. 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 were observed. This antitumor dose response (with folate supplementation) is identical to the dose response that was observed for MTA on mice fed with SD. These data suggest that folate supplementation not only modulates the toxicity but also slightly enhances the antitumor response of MTA.

(…)

REFERENCES

(…)
35. Worzalla JF, Self TD, Theoblad KS, Schultz RM, Mendelsohn LG, Shih C. Effects of folic acid on toxicity and antitumor activity of LY231514 multitargeted antifolate (MTA). *Proc Am Assoc Cancer Res* 1997; 38:478.
(…)

2.9.6. In the journal '*Seminars in Oncology'* (Vol. 26, No. 2, Suppl. 6 (April), 1999, p. 3-10) an article entitled '*An Overview of Folate Metabolism: Features Relevant to the Action and Toxicides of Antifolate Anticancer Agents'* by H. Calvert (hereinafter: Calvert) was published, with the following passages:

Page 7, right column, halfway through:

In addition, selective inhibitors of GARFT, the first folate-dependent enzyme involved in the pathway of de novo purine synthesis, have been developed. Examples of these are lometrexol and LY309887 (Fig 4). These compounds have good antitumor activity in preclinical systems with the suggestion that their activity may be preserved in tumor cells that have a nonfunctional p53 pathway. The clinical toxicity of many antifolates is, not surprisingly, affected by the pretreatment folate status of the patient. In the case of the GARFT inhibitors, the effect of the folate status is particularly marked, with the maximum tolerated dose being at least 10-fold higher in patients who have received folate supplementation compared with those who have not.[15]

Pag. 8:

Clinical Measurement of Functional Folate Status

Although the effect of folic acid supplementation on reducing the toxicity of antifolate drugs (particularly the GARFT inhibitors) is clear, it always has been difficult to correlate antifolate-induced toxicity with pretreatment folate levels. One possible explanation for this is that the folate levels do not adequately reflect the functioning of folic acid within proliferating cells at the time of measurement. In addition to the pathways discussed so far, folic acid is also involved in cellular methylation reactions by virtue of its role in methionine synthesis. CH_2FH_4 can be reduced to 5-methyltetrahydrofolate (Fig 1). This is a substrate for the enzyme methionine synthase, which uses the methyl group to convert homocysteine to methionine. Methionine in turn takes part in cellular methylation reactions regenerating homocysteine. Methionine synthase is B_{12}-dependent but also uses 5-methyltetrahydrofolate as the co-substrate. Thus, any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine[16]

Pag. 9:

OVERVIEW OF FOLATE METABOLISM 9

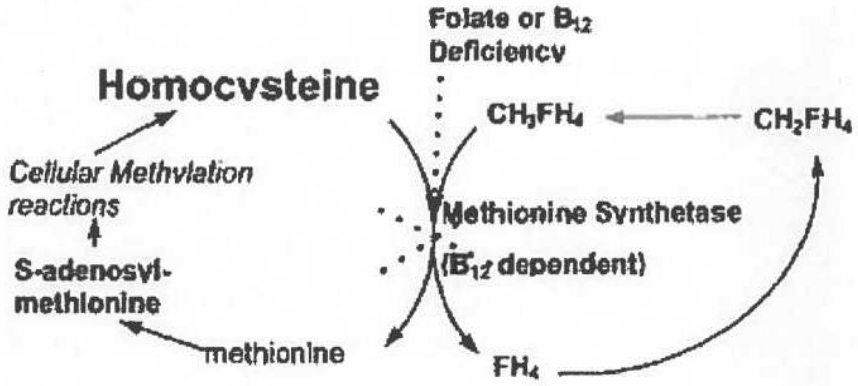

Fig 8. Role of 5-methyl tetrahydrofolic acid: a reduction in functional folate increases plasma homocysteine levels.

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

LY231514 (MTA)

MTA was developed by Eli Lilly and Company (Indianapolis, IN), initially as a TS inhibitor. However, it rapidly became clear that, unlike any of the other antifolates discussed, MTA is capable of inhibiting two other enzymes involved in folate metabolism, GARFT and DHFR (see Mendelsohn et al, this supplement). MTA also has a broad spectrum of preclinical activity, displays different patterns of cross-resistance to other antifolates, and has an encouraging level of activity documented in early phase II clinical trials.[18] It is possible that its capability of inhibiting more than one locus contributes to these results by increasing the spectrum of biochemical profiles of tumors potentially sensitive to the drug and discouraging the development of drug resistance. Reports that follow in this supplement address these issues in detail.

CONCLUSIONS

Naturally occurring folates have complex metabolic pathways and are involved in a number of biochemical processes essential to life, including cell proliferation. In addition to their direct role in various metabolic pathways, a number of other phenomena will significantly affect the actions both of natural folates and their analogues acting as antifolates. These include cell membrane transport, the formation of polyglutamates, and the pretreatment folate status of the patient concerned. The very complexity of the processes involved suggests ways in which the action of antifolates could be tuned to have a selective advantage against tumors compared with normal tissues. Several clinically active drugs have already been developed. LY231514 (MTA) may establish itself as an important addition and advance those currently available.

3. The dispute

3.1. Sandoz claims nullification of the Dutch part of EP 508 and that Lilly, based on article 1019h CCP[4], be ordered to pay the estimated costs of the proceedings plus interest, with the judgment being declared provisionally enforceable as far as possible.

3.2. Sandoz bases this, in summary, on the following grounds. Claims 1 to 9 and 12 to 14 of EP 508 are invalid because of a lack of novelty in the light of Worzalla, to which claims 10 and 11 add nothing inventive because the claimed variants (with intramuscular or oral administration respectively) are obvious for the average person skilled in the art. The patent is also invalid because of a lack of inventive step, primarily assuming Jackman in combination with common general knowledge about the methyl-folate *trap* but also assuming Calvert in combination with common general knowledge about the methyl-folate trap, at least the common general knowledge as evidenced by Jackman, or assuming Worzalla in combination with Jackman or Calvert. These documents render claim 2 invalid, and with it the broader claim 1 (which is not limited to pemetrexed and vitamin B12), and the additional features of the following claims add nothing to them.

3.3. Lilly put forward substantiated defence.

3.4. The assertions of the parties, insofar as significant, will be dealt with here below.

4. The assessment

Jurisdiction

4.1. Based on article 24(4) Brussels I bis Regulation[5], the District Court has international jurisdiction, and based on Section 80(1)(a) Patents Act 1995, territorial jurisdiction to hear the claim.

Objection to exhibits

4.2. Lilly has objected to admission of the exhibits EP39 to EP45 not announced in the summons, because of the absence of an explanation on the relevance of those exhibits in the corresponding document of 14 June 2017. The District Court dismisses that objection for exhibits EP39 and EP42 to EP45. Sandoz did provide an explanation to these exhibits by document of 29 November 2017. It is difficult to see that Lilly, which has not asserted that it cannot respond to this adequately, is impaired in its defence because of this. With regard to exhibits EP40 and EP41 the objection is founded. That these exhibits were all known from the European patent granting proceedings respectively Dutch preliminary relief proceedings, as Sandoz has argued, does not alter the fact that with a view to Lilly's ability to conduct a proper defence and

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4 Dutch Code of Civil Procedure.

5 Regulation (EU) 1215/2012 of the European Parliament and of the Council of 12 December 2012 on jurisdiction and the recognition and enforcement of judgments in civil and commercial matters.

the information to the District Court, at least before the session it should have made clear with what purpose it was submitting those exhibits into these proceedings.[6] Now that it has failed to do so (even after it was pointed out), EP40 and EP41 as exhibits of Sandoz are refused because of violation of due process.

4.3. In the event that Lilly's objection is honoured, Sandoz has in turn objected to exhibit GP16, asserting that GP16 was known from the patent granting procedure and therefore could have been submitted earlier, so that this exhibit in accordance with the reasoning applied by Lilly with regard to the exhibits referred to in legal ground 4.2. must be refused. However, the comparison does not hold water. As is apparent from legal ground 4.2., the exhibits EP40 and EP41 contested by Lilly are not refused because they could previously have been submitted, but because the purpose of their submission was not mentioned. That is not relevant with regard to GP16. In view of this and in the absence of any harmed interest on the part of Sandoz, the objection is dismissed.

Technical background

4.4. Prior to the assessment of the novelty and inventive step objections made by Sandoz against EP 508, an undisputed technical background related to folates, the so-called methyl-folate trap and antifolates, derived from the parties' documents is given here below.

4.4.1. Folate is an essential vitamin from the B complex of vitamins. Humans depend on external sources (diet or dietary supplements) for folates. Natural folate variants are found in spinach, Brussels sprouts, broccoli and cabbage for example. Folic acid is a synthetic variant and the most stable form of folate, which is added to many foods. Folic acid is converted in the body into other folate forms. The most common folate variant in blood plasma is 5-methyl-tetrahydrofolate (MTHF).

4.4.2. Folate plays a role in several biochemical processes in the cells in the body, including in the DNA cycle, which is the basis for cell division. Within the DNA cycle different folate variants function as so-called cofactors of enzymes that (through a series of reactions) are needed for forming DNA (DNA synthesis). A cofactor is needed to give an enzyme biological activity (the cofactor acts as an on/off button as it were). Among the most important folate-requiring enzymes involved in the metabolism of a cell are Thymidylate Synthase (TS), GlycinAmide Ribonucleotide FormylTransferase (GARFT) and DiHydroFolate Reductase (DHFR).

4.4.3. Folates also play a role in the methylation cycle in the body. In that cycle, the MTHF folate variant is needed for converting the substance homocysteine into the substance methionine. Methionine is needed to make proteins.

4.4.4. The enzyme methionine synthase is involved in the conversion of homocysteine to methionine. This enzyme also plays a role in the DNA-cycle, in the conversion of

6 Supreme Court 10 March 2017, ECLI:NL:HR:2017:404

MTHF to tetrahydrofolate (THF), which folate is needed for further steps in DNA synthesis.

4.4.5. A cofactor for methionine synthase is methylcobalamin. Methylcobalamin is formed by the methyl group of MTHF and cobalamin, i.e. vitamin B12.
In the human body vitamin B12 is the only acceptor of the methyl group of MTHF and MTHF is the only donor of the methyl group to vitamin B12. After vitamin B12 has taken over the methyl group of MTHF methylcobalamin is formed. By the formation of methylcobalamin MTHF is removed from the methyl group and THF is formed (see paragraph 4.4.4.) which is needed in the DNA-cycle. In the methylation cycle, methylcobalamin is able to 'pass on' the methyl group to homocysteine with the help of the enzyme methionine synthase. Homocysteine is converted to methionine with this methyl group.

4.4.6. In the event of a vitamin B12 deficiency, there is too little 'methyl acceptor' and the 'methyl donor' MTHF 'stays with the methyl group'. In other words, a vitamin B12 deficiency prevents the reaction of MTHF to THF and THF remains 'trapped' in the methyl group in the form of MTHF as it were. Because the folate is 'trapped' it cannot fulfil a useful function, so that in such a situation this is also referred to as a pseudo-deficiency of folate or a functional deficiency of folate (it is present, but in the wrong form). This is called the methyl-folate *trap*.

4.4.7. An antifolate is an analogue of folate. Antifolates compete with folates as it were and bind to enzymes such as TS, GARFT and DHFR instead of folates, meaning their functioning is inhibited. As a result, the DNA formation and hence cell division are interrupted, amongst other things by rapidly dividing cells such as tumour cells. Within the oncology field different antifolates are used as medication or are researched as anti-cancer drugs. The antifolate methotrexate (which was developed at the end of the 1940s and approved for medical use at some point) binds to DHFR. At the end of the 1990s the antifolate raltitrexed (brand name: Tomudex) was approved for medical use for the treatment of colon cancer. Raltitrexed binds to the enzyme TS. The antifolate lometrexol binds to the enzyme GARFT. Pemetrexed, the antifolate developed by Lilly, binds to TS, GARFT and DHFR. Pemetrexed is therefore referred to as the Multi Target Antifolate drug (MTA).

4.4.8. Because antifolates not only interrupt the formation of cancer cells, but also the formation of normal cells, in particular rapidly dividing cells in the bone marrow and gastrointestinal tract, their use can lead to severe toxic effects (side effects).

Novelty - Worzalla

4.5. Worzalla is a study into the effect of folic acid on the side effects (toxicity) and anti-tumour efficacy of pemetrexed in mice with implanted tumour cells. In the scope of this study, a group of mice was kept on a diet with low folic acid levels (*folic acid deficient diet or low folate diet*) and another group of mice was kept on a standard diet. In the summons and its document of 14 June 2017 - just as in the previous preliminary relief proceedings – Sandoz has taken the position that Worzalla anticipates claims 1 to 9 and 12 to 14 of EP 508 because - in short -

in the research some of the mice (namely those on the standard diet) were fed 'Purina Chow #5001'. This feed contains twice as much vitamin B12 as was considered usual according to nutritional standards for laboratory mice at the time, evidently, according to Sandoz, in the belief that an adequate amount of vitamin B12 was needed.

4.6. Lilly has argued with reasons in statement of defence that the second medical use claims (and "mutatis mutandis" the claims 12 to 14) of EP 508 derive their novelty from the intended new therapeutic combined use of pemetrexed disodium and vitamin B12 (and - in short[7] - folic acid for claim 2), which therapeutic use is not disclosed in Worzalla at all. The composition of the feed that Worzalla gave to the mice, asserted by Sandoz (and disputed by Lilly) is therefore irrelevant according to Lilly. Sandoz has not contradicted this in turn. It has not submitted any additional exhibits in this respect nor revisited the reasoned challenge of its assertions by Lilly in oral arguments. It has not further substantiated its assertion that 'evidently the idea was that administration of an adequate amount of vitamin B12 was needed'. Sandoz has thus in no way at all explained from what the person skilled in the art derives that some amount of vitamin B12 - if any at all - was deliberately administered by the researchers of the Worzalla study, i.e., for therapeutic purposes. Its argument is therefore dismissed as insufficiently substantiated.

4.7. Claims 1 to 9 and 12 to 14 of EP 508 can therefore be considered novel. Consequently, the District Court does not reach the assertion that claims 10 and 11, in the absence of novelty of the preceding claims, are not inventive.

Inventive step - Jackman

4.8. Sandoz' primary inventive step attack assumes Jackman as a starting point and is aimed at claim 2 of EP 508, subject to the proviso that - as acknowledged by Lilly - if claim 2 is invalid, that also applies for claim 1. Sandoz' position can be summarised as follows:

> 1) The combination of pemetrexed and folate is prior art because that combination is revealed in chapter 8, paragraph 2.6 of the Jackman manual. Jackman indicates that folic acid reduces the side effects of pemetrexed and that the efficacy is not affected:
>
> *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 were observed. (...)*
> *These data suggest that folate supplementation not only modulates the toxicity but also slightly enhances the antitumor response of MTA.*

[7] In addition to folic acid, claim 2 also claims other folate forms but following Lilly the District Court will only speak of folic acid.

The person skilled in the art knows therefore that the administration of folate with pemetrexed is useful. This doctrine is also included in numerous other publications.

2) It is common general knowledge that vitamin B12 is needed in order to keep folate functional. Without vitamin B12 the folate is caught in the methyl-trap and is not functional.

3) Therefore, it is obvious to investigate with a *reasonable expectation of success* whether in addition to the administration of folate the administration of vitamin B12 also contributes to reducing the side effects of pemetrexed. Claim 2 of EP 508 is therefore a given.

4.9. One of Lilly's defences is that Sandoz' reasoning is based on the erroneous premise that the person skilled in the art on the priority date would have reason to administer folic acid to cancer patients in combination therapy with pemetrexed. According to Lilly, Jackman is merely a compilation of articles and not a manual, and as apparent from the references to chapter 8 not based on any publication after 1997. In addition, paragraph 2.6 of Chapter 8 refers to the Worzalla study, of which in 1997 only the Worzalla abstract was published. The person skilled in the art would therefore look beyond Jackman on the priority date. He would also consider the underlying publications of paragraph 2.6 of chapter 8 and the follow-up studies and then know that using folic acid is at the expense of the efficacy of pemetrexed, which leads the person skilled in the art away from that combination therapy and the invention.

4.10. This defence succeeds. The District Court considers the following on this. Here it will assume with Sandoz that the person skilled in the art is a team consisting of an oncologist, who cancer patients see at the clinic, and a biochemical pharmacologist with knowledge of folates and antifolates conducting research.

4.11. Chapter 8, paragraph 2.6 of Jackman is a discussion of research into the influence of prior administration of folic acid on the toxicity of pemetrexed in the fight against tumours. In itself it is correct, as Sandoz asserts, that Jackman discloses the combination of folic acid with pemetrexed. Along with Lilly, the District Court also believes that because of the date in combination with the nature and content of the research discussed in paragraph 2.6 of Chapter 8, Jackman is a too limited and therefore not a realistic starting point for the assessment of the inventive step of EP 508.

4.12. Paragraph 2.6 of chapter 8 is part of the prior art but the content does not reveal the prior art on the priority date when it comes to the combination of pemetrexed and folic acid, and the person skilled in the art knew that. It is not contested after all that Jackman is a compilation of articles and that chapter 8 is not based on any publication after 1997. That also applies for paragraph 2.6, which contains a discussion of the Worzalla study. In endnote 35, Jackman refers to the Worzalla abstract published in March 1997. However, at the time of the publication of Jackman (and therefore also on the priority date), the full Worzalla study had already been published. When reading Jackman, the person skilled in the art would therefore not only read the abstract but also the Worzalla study. He would also see that Worzalla only contains a preclinical study on the effects of pemetrexed and folic acid

on a specific mouse model (see also legal ground 4.15.), while on the priority date (almost three years later) there were also publications of the clinical follow-up trials of treatment with pemetrexed and folic acid on humans available in the form of Hammond I and II. The person skilled in the art would likewise consider these publications (hereinafter together also: the Hammond study[8]). Were this to be different, then in the inventive step assessment (a part of) the common general knowledge attributed to the person skilled in the art in respect of the combination of pemetrexed and folic acid disclosed in Jackman on the priority date can simply be ignored.

4.13. The starting point for the inventive step assessment is not so much Jackman therefore, but the prior art known to the person skilled in the art in the research into the combination of folic acid and pemetrexed on the priority date, as apparent from the Worzalla study discussed in Jackman (Worzalla abstract and Worzalla study) and the Hammond study elaborating on it. That prior art is as follows.

4.14. As already considered in legal ground 4.5. the Worzalla study discussed the result of pre-clinical research with mice in which the effect of prior treatment with folic acid has been studied. It shows that by prior administration of folic acid pemetrexed is less toxic, in the sense that higher doses of pemetrexed are possible without mortality. At the same time, this study shows that the administration of folic acid decreases the efficacy of pemetrexed if the dose is not increased. It is concluded after all (under '*Discussion'*, see 2.9.2): "*Oral folic acid dramatically decreased the toxicity of LY231514 and preserved antitumor activity (albeit at higher dose levels) in these mice*" (emphasis, District Court). The Worzalla study refers to figure 2, where it can be read that in mice on a low folate diet, which received no folate supplement, an anti-tumour action of 100% was measured at doses of between 0.3 and 1 mg/kg/day pemetrexed. To obtain the same efficacy in mice on the same low folate diet with folate supplement, doses of more than 30 mg/kg/day were needed according to this figure.

4.15. It can be further deduced from the Worzalla study that for the research which the results laid down in figure 2 concern, a highly sensitive cancer cell line (L5178Y/TK-/HX) for pemetrexed is used (see table II of Worzalla in which the difference in efficacy is shown compared to the treatment of mice with a 'wild type' tumour). Through its expert, Calvert, Lilly has undisputedly argued with regard to the use of this special cell line that it is not suitable to predict the relationship between toxicity and efficacy: "*It is a good model to compare the efficacy between test compounds. It is a poor model to predict the relationship between toxicity and efficacy in a normal mouse and even less so in humans*[9]*."* The Worzalla study even says itself that the mouse models according to the researchers have "*poor predictive value for antifolate toxicity*".

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[8] The District Court understands that Hammond I and Hammond II refer to a different stage of the same study, which at the time of Hammond I concerned 21 patients and at the time of Hammond II 33 patients. In the Hammond study, it is concluded that administration of folic acid seems to make higher dosages of pemetrexed possible, with Hammond II specifically making the link with improvement of the toxicity: "*FA supplementation appears to permit MTA dose escalation by ameliorating toxicity*".

[9] Statement of Professor H.J. Calvert of 5 January 2018 (Calvert II, GP19) no. 7.

4.16. Because of the Worzalla study, the person skilled in the art knows on the priority date that the conclusion cited by Sandoz from Jackman that "*these data suggest that folate supplementation not only modulates the toxicity but also slightly enhances the antitumor response of MTA*" must be balanced, in the sense that folic acid reduces the toxicity of pemetrexed and thus makes a higher dose of pemetrexed possible, but that the administration of folic acid at the same time also requires a higher dose of pemetrexed to get the same level of efficacy. It is questionable whether that also applies if pemetrexed is administered to humans in combination with folic acid.

4.17. When the Hammond study is added to this, the person skilled in the art finds confirmation for the idea that the addition of folic acid reduces the side effects of pemetrexed, but not for the idea that that addition could affect the efficacy (*anti-tumour response*) of pemetrexed positively. According to the description, the Hammond study concerns a phase I study in which cancer patients were (pre)treated with folic acid for doses of pemetrexed of 600, 700, 800 and 925 mg/m2, after an earlier phase I study (referred to by the parties as the Rinaldi study, hereinafter: Rinaldi) with pemetrexed but without administration of folic acid had shown that specific side effects did not allow a dosage greater than 500-600 mg/m2.

4.18. Where the efficacy of pemetrexed is concerned, Hammond I says that a '*partial response'* was only observed in one patient (out of 21 patients; this number was not higher when the number of patients was extended to 33 in Hammond II), while in Rinaldi - according to Hammond I - '*major antitumor response'* (in 10 of the 37 patients) was still observed. Sandoz has argued that the studies referred to are two different studies with different set ups and that in the absence of randomisation of the patient population they are not comparable, but then it ignores that those studies are compared by Hammond and are also related to each other because of the dosage of pemetrexed. This means the comparison, erroneous or not, is part of the disclosed outcome of the Hammond study. In addition, Sandoz has not, at least not sufficiently, disputed Lilly's assertion that in phase I studies with cancer patients the response is always assessed and that the mention of only one partial response versus '*major anti-tumour response'* at least would be a sign for the person skilled in the art that the administration of folic acid might be at the expense of the efficacy of pemetrexed, as the Worzalla study also showed.

4.19. The other publications cited by Sandoz also do not disclose that the combination of pemetrexed and the (pre)treatment with folic acid leads to reduced toxicity without the efficacy of pemetrexed being reduced. At the hearing, when asked, Sandoz acknowledged that the review article by Calvert says nothing about an effect of the pre-treatment with folate on the efficacy of an antifolate. Calvert only describes the antitumour action of pemetrexed and that the related toxicity can possibly be predicted by measuring the homocysteine levels in the plasma prior to treatment. The combination of folic acid and pemetrexed is not disclosed in Calvert. The publication of Adjei[10]

[10] A. A. Adjei, *'A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer',* J. Clin Pharmacol, 1999, 48, pp. 265-277, submitted by Sandoz as exhibit EP19.

by reference in endnote 53 falls back on the Hammond study and sees the outcomes achieved as a success. Here above, however, it was already considered that there still needs to be some haggling about those results in the sense that (pre)treatment with folic acid leads to a reduced efficacy of pemetrexed. The article by Cripps[11] bases the assertion that "*A phase I study is underway investigating the combination of MTA and folic acid. High homocysteine levels [18] may be a predictor to toxicity or MTA and it is possible that when MTA is used in combination with folic acid, toxicity may be eliminated with no compromise in efficacy"* in endnote 18 on 'Unpublished data - Eli Lilly and Company', which, having regard to the point in time, as Lilly has undisputedly argued, must have been either the Worzalla or the Hammond study. There were no other publications available at that time. These studies were already discussed here above.

4.20. The prior art in the research into the combination of folic acid and pemetrexed for cancer patients on the priority date is such that folic acid works well as an antidote to counteract the side effects of pemetrexed, but that at the same time folic acid reduces the efficacy of pemetrexed. On the priority date, the person skilled in the art has the knowledge that increasing the dose to compensate for the reduced efficacy has been studied, but that given the low response in the Hammond study the added value thereof has not been demonstrated.

4.21. Moreover, it can be undisputedly assumed that it may be a concern for the person skilled in the art that higher doses of pemetrexed would have adverse effects on kidney function. The Hammond study shows that at least 7 of the 33 patients had a decrease in kidney function in the form of a 'decrease in creatinine clearance', which is referred to as significant in Hammond II (significant decrease in CrCl). Referring to the statements of its expert Jackman (and confirmation thereof by its expert Calvert), Lilly has argued that the person skilled in the art would understand that folic acid would not protect against this kidney toxicity. Sandoz has put forward nothing against this.

4.22. The District Court therefore disregards Sandoz' assertion that the administration of folic acid in a combination therapy with pemetrexed was prior art on the priority date, let alone that the application of that therapy - as Sandoz has also argued - could be considered as being part of the common general knowledge on that date. The District Court also takes into consideration that the documents discussed concerning the combination of pemetrexed and folic acid (Worzalla and Hammond) date back to 1998 and that if they (potentially) would reveal a successful combination therapy for cancer, it would be expected that that combination was applied in the treatment of cancer on the priority date, at least that further studies would have taken place for that application. It has neither been argued nor become evident that that was the case. On the contrary, Lilly has undisputedly argued that no folic acid was administered in the follow up clinical phase II trial with pemetrexed (written pleadings, marginal number 2.19 under (c)).

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[11] C. Cripps et al., *'Phase II study of first-line LY231514 (multi-targeted antifolate) in patients with locally advanced or metastatic colorectal cancer: An NCIC Clinical Trials Group Study*', Annals of Oncology, 1999. 10, pp. 1175-1179, submitted by Sandoz as exhibit EP20.

4.23. That the person skilled in the art reads in (among others) Jackman that the administration of folates also reduces the toxicity of an antifolate such as lometrexol (see Jackman paragraph 2.6 '*A similar effect has been observed for antipurine antifolates such as lometrexol'*), as Sandoz has argued, does not alter the above, aside from the fact that Sandoz has not, at least not sufficiently, contested Lilly's argument that the Laohavinij[12] study, available on the priority date, which experimented with adding folic acid to the treatment regimen of lometrexol (which has a different operating mechanism to pemetrexed), taught the person skilled in the art that the addition led to a reduced efficacy of lometrexol ('*only one objective partial response has been observed'* in a total of 43 patients), that the person skilled in the art was aware on the priority date that lometrexol had been removed from the market due to toxicity problems (which could not be resolved even with folic acid) and that for the only two antifolates permitted in Europe, methotrexate and raltitrexed, (pre)treatment with folic acid was discouraged in the medication leaflet.

4.24. Since the combination therapy of pemetrexed and folic acid on the priority date cannot be regarded as a given for the person skilled in the art, there is no ground for Sandoz' argument as set out in legal ground 4.8. and the District Court will not deal with its arguments relating to vitamin B12. In the light of the documents discussed, claims 2 and 1 must be deemed inventive. That also applies for claims 3 to 11. Sandoz has not substantiated why this would be different for independent claim 12 and the claims 13 and 14 dependent on it so that those claims are also considered valid.

Inventiveness – Worzalla

4.25. Sandoz has set up a separate inventive step attack using Worzalla (in combination with Jackman or Calvert) asserting that Worzalla teaches the person skilled in the art that folic acid must be administered in combination therapy with pemetrexed. As considered here above (under legal grounds 4.14. to 4.16.) however, that is not what was disclosed in Worzalla. The ground for this inventive step attack is also lacking.

Inventive step – Calvert

4.26. Lilly disputed the inventive step attack using Calvert included in the summons with reasons in its statement of defence. Having regard to what has been considered in the preceding legal grounds, Lilly has rightly argued that the starting point used by Sandoz that the combination therapy of pemetrexed and folic acid can be considered part of the prior art is incorrect. Calvert does not say any different (cf. legal ground 4.19). Sandoz has also incidentally not further substantiated the inventive step attack based on Calvert so that its assertions in this respect can be dismissed as insufficiently substantiated.

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[12] A publication by S. Laohavinij e.a. in *'Investigational New* Drugs' (14: 325-335, 1996) entitled *'A Phase I clinical study of the antipurine antifolate lometrexol (DDATHF) given with oral folic acid'* (submitted by Lilly as GP07 - Annex 3).

Conclusion

4.27. Since the above means that none of Sandoz' inventive step attacks succeeds, its claim for nullification of the Dutch part of EP 508 is dismissed.

4.28. This means the District Court reaches a different outcome than the Bundespatentgericht in its ruling of 17 July 2018, in which the German part of EP 508 was nullified due to lack of inventive step. The Bundespatentgericht based its decision on partly other combined prior art than relevant in these proceedings.[13] The debate also seems to have been different in other respects (for example, the ruling does not show that the assertion was made that increasing the dose of pemetrexed leads to kidney toxicity as well as that no folic acid was administered in the follow up clinical phase II trial of pemetrexed).

Costs of the proceedings

4.29. As the party found to be in the wrong, Sandoz is ordered to pay the costs of the proceedings, which on the side of Lilly, in accordance with the agreement made by the parties, are estimated at €300,000. The claimed statutory interest and provisionally enforceable statement will be allowed as undisputed as explained here below.

5. Decision

The District Court

5.1. dismisses the claim;

5.2. orders Sandoz to pay the costs of the proceedings, on the side of Lilly to date, estimated at €300,000, plus the statutory interest with effect of 14 days after service of this judgment until the date of full payment;

5.3. declares this judgment to be provisionally enforceable with regard to the costs of the proceedings.

This judgment was given by J.Th. van Walderveen, M. Knijff and C.T. Aalbers and read out in open court on 16 January 2019.

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[13] Niyikiza, amongst others, has been assumed, which Sandoz precisely stayed away from in these proceedings, see written pleadings Eli Lilly, marginal number 4.2