

judgment

THE HAGUE COURT OF APPEAL

Civil-Law Division

Case number : 200.261.833/01

District Court case number: C/09/541424/ HA ZA 17-1097

judgment of 27 October 2020

in the matter of

Eli Lilly and Company,

with its registered office in Indianapolis, Indiana, United States of America,
appellant in the principal appeal,
respondent in the cross-appeal,
hereinafter referred to as: Eli Lilly,
counsel: K.A.J. Bisschop practising in Amsterdam,

versus

Fresenius Kabi Nederland B.V.,

with its registered office in 's-Hertogenbosch,
respondent in the principal appeal,
respondent in the cross-appeal,
hereinafter referred to as: Fresenius,
counsel: P.L. Reeskamp practising in Amsterdam.

1. The proceedings

1.1. The Court of Appeal has taken cognisance of the following case documents:

- the case file of the proceedings in the first instance;
- the Summons to appear in appeal proceedings of 19 June 2019;
- the Statement of Appeal containing an increase of claim, with exhibits;
- the Defence on Appeal, also Statement of Appeal in the cross-appeal, with exhibits;
- the Defence on Appeal in the cross-appeal, with exhibits;
- the document containing additional exhibits also containing a change of claim submitted by Lilly, with exhibits 79 through 89;
- the document containing Fresenius's additional exhibits, with exhibits 44 through 52;
- the document containing additional exhibit submitted by Eli Lilly, with exhibit 90;
- notice from Mr Lilly's lawyer that the parties have reached an agreement on the amount of the costs of the appeal proceedings; and - de oral hearing of 20 January 2020.

1.2. Further to a request from Fresenius, the Court of Appeal decided to extend the time available to the parties to address the court during the oral hearing from 45 minutes in the first stage for each side – which is customary in patent cases – to 60 minutes in the first stage for each side. The Court of Appeal rejected any requests from Fresenius to further extend the time allowed for addressing the court.

1.3. Judgment was scheduled for today.

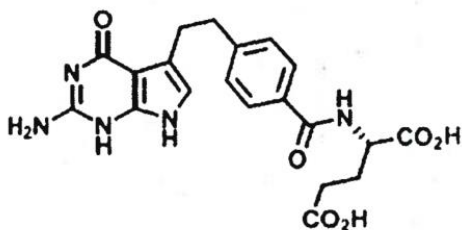
2. The facts

2.1. The facts established by the District Court in the judgment of 19 June 2019 are not in dispute. The Court of Appeal, too, will take these facts as a starting point, in respect of which recent judgments have been added to the overview of case law. This case concerns the following.

Pemetrexed, Lilly and Alimta®

2.2. Pemetrexed is an antifolate. Antifolates are antineoplastics. This means that they prevent the formation of (cancer) tumours. Antifolates not only have an effect – inhibiting or otherwise – on the growth of fast-growing cancer cells, but also on the growth of healthy cells. As a result, treatment with an antifolate can cause serious adverse reactions (toxicity).

2.3. Due to the presence of two $-CO_2H$ groups, the substance pemetrexed is a free acid (diacid) (hereinafter: pemetrexed diacid) which has the following molecular structure:



The CAS (Chemical Abstract Service) number of pemetrexed diacid is 137281-23-3.

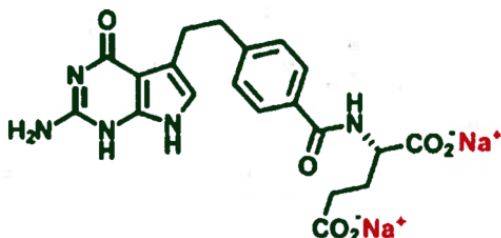
2.4. When pemetrexed diacid is mixed with an aqueous solution, the hydrogen atoms indicated in red are separated from the rest of the molecule as positively charged ions, which is then a negatively charged ion (also known as anion). Only the anion is responsible for the efficacy and toxicity of the antifolate.

2.5. Lilly is part of the Lilly group that engages in the development and trade of, and research into new medicinal products.

2.6. Lilly is marketing the pemetrexed disodium containing Alimta®, which is indicated for the treatment of certain types of lung cancer (tumour growth).

2.7. Alimta® is in the form of a freeze-dried powder for concentrate for solution for intravenous infusion. The excipients mannitol, hydrochloric acid and sodium hydroxide have been used for the formulation. In the "Summary of Product Characteristics" (hereinafter: SmPC) of Alimta® states that the product should be diluted in a physiological saline solution for infusion. Alimta® should be administered in combination with vitamin B12 and folic acid.

2.8. The molecular structure of Alimta® is similar to that of pemetrexed diacid, except that pemetrexed disodium has two CChNa groups instead of the two CO₂H groups (see 2.3). A salt form of pemetrexed is formed by the sodium ions. The structural formula is as follows:



The CAS number of pemetrexed disodium is 150399-23-8.

2.9. When Alimta® is mixed with an aqueous solution for intravenous infusion, the sodium atoms indicated in red are separated as cations from the rest of the molecule and the (green-coloured) negatively charged pemetrexed anion remains. Here, too, only the anion is responsible for the efficacy and toxicity of the antifolate.

2.10. It is not possible to manufacture a form of administration of pemetrexed that consists only of the anion; only a neutral substance can be used and this implies the presence of a cation (a positively charged ion, with which a salt is formed) or hydrogen (with which diacid is formed).

2.11. The antifolate pemetrexed, i.e. both the diacid and pharmaceutically acceptable salts of pemetrexed such as the disodium salt, was initially protected by EP 0 432 677 (hereafter referred to as: EP 677) of which Lilly was (co-)holder. EP 677 is the basic patent for Supplementary Protection Certificate 300181 for "pemetrexed, optionally in the form of a pharmaceutically acceptable salt". The certificate was in force until 9 December 2015.

The patent (EP 508)

2.12. Lilly is the holder of European patent 1313 508 BI (hereinafter: EP 508), titled "*Combination containing an antifolate and methylmalonic acid lowering agent*" (in Dutch '*Samenstelling welke een antifolaat en methylmallonzuur verlagend middel bevat*'). EP 508 was granted on 18 April 2007 in response to an international application dated 15 June 2001 under number PCT/US2001/014860 (hereinafter: the PCT application or the original application) published as WW 02/02093 A2 (hereinafter: WO 093). In addition, priority was invoked of US 215310 P of 30 June 2000, US 235859 P of 27 September 2000 and US 284448 P of 18 April 2001.

2.13. EP 508 contains two independent claims (1 and 12) and independent claims (2 through 11 and 13 through 14). In the original English language, the claims 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.

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.

2.14. In the official 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.

2.15. The patent specification provides – in so far as relevant here – 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®, 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 myelosuppression 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 [sic] 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.

(...)

[0010] The invention specifically provides the use of the antifolate 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 a methylmalonic acid lowering agent selected from vitamin B12 and pharmaceutical derivatives thereof.

[0011] The invention also specifically provides the use of the antifolate 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 a methylmalonic acid lowering agent selected from vitamin B12 and pharmaceutical derivatives thereof and a FBP binding agent 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.

(...)

[0016] The current invention concerns the discovery that administration of a methylmalonic acid lowering agent such as vitamin B12 or a pharmaceutical derivative thereof, in combination with an antifolate drug such as pemetrexed disodium reduces the toxicity of the said antifolate drug.

(...)

[0022] The terms "antifolate" and "antifolate drug" generally refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. The "antifolate" or "antifolate drug" for use in this invention is Pemetrexed Disodium (ALIMTA®), as manufactured by Lilly & Co.

2.16. By letter of 8 January 2003, Lilly's in-house patent agent, Dr I.J. Burnside (hereinafter: Burnside) requested the European Patent Office (EPO) to consider the PCT application on the basis of the documentation under which the International Preliminary Examination was carried out. In so doing, he replaced the original claims from the PCT application by a new set of claims (1 through 17), of which new claim 1 read as follows:

1. Use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate

2.17. By *Communication* of 9 March 2004, the *examiner* of the EPO indicated, among other things, that the subject matter of the new claims 1 through 9, 11 through 14 and 16 lack novelty in the light of the documents D1 (EP 0 546 870) and D2 (US 5 405 839) because –briefly put – the use of an antifolate,

namely 5-fluorouracil and methotrexate, in combination with vitamin B12 (a *methylmalonic acid lowering agent*) had already been disclosed therein.

2.18. By fax of 23 December 2004, Burnside filed another set of claims and informed the EPO as follows in so doing:

In reply to the Communication pursuant to Article 96(2) EPC dated 9 March 2004 I attach new claims 1-16 to replace claims 1-17 previously on file. I also attach amended description pages 2, 2a, 3, 4, 4a and 6 to replace description pages 2 to 4 and 6 presently on file.

Amendments

The Applicant, having reviewed the scope of the application and in order to expedite the application proceeding to grant, has elected to amend the claims so as to more closely reflect the specific examples provided. The present amendments are made without prejudice to the Applicant's right to obtain protection for other patentable subject matter in one or more divisional applications.

Claims 1-12 have been refocused on the use of the antifolate compound pemetrexed. Basis can be found at page 2 line 6-7 and page 6 line 16 of the application as filed.

The term "methylmalonic acid lowering agent" has been replaced by "vitamin B12 or a pharmaceutical derivative thereof". Basis for this can be found page 6 lines 19-21 and page 7 line 5 of the application as filed.

(...)

Novelty

There is no disclosure in any of documents D1-D3 of the invention as presently claimed. In particular D1 and D2 do not relate to pemetrexed. D3 does not disclose or relate in any way to the use of vitamin B12.

(...)

2.19. Claims 1,4, 13 and 16 of the changed set of claims filed by Burnside read as follows, in so far as relevant here:

1. Use of pemetrexed 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.

4. Use according to any one of claims 1 to 3 wherein pemetrexed is pemetrexed disodium.

13. A product containing pemetrexed, vitamin B12 or a pharmaceutical derivative thereof and, optionally, a folic binding protein agent (...) as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumor growth.

16. A product according to any one of claims 13 to 15 wherein pemetrexed is pemetrexed disodium.

2.20. By *Communication* of 17 May 2005, the EPO responded to this as follows, in so far as relevant

Amendments (Art. 123(2) EPC)

The amendments filed with letter 23.12.2004 do not comply with the requirements of Art. 123 (2) EPC in so far as they introduce subject matter beyond the content of the originally filed documents.

The amendments concerned are the following:

The subject matter of claims 1-16 and description pages 4, line 18- page 4a.

The subject matter of present claims 1 reading "use of pemetrexed..." and claim 13 "a product containing pemetrexed..." do not find base in the application documents as filed. The term "pemetrexed" in the wording of these claims and the corresponding passages on amended description is certainly a distinct compound (CAS Registry number 137281-23-3) of the "pemetrexed disodium" (CAS Registry number 150399-23-8) expressed on original document description page 2, line 6 and page 6, line 16. Said amendment beyond the content of the original document is therefore not allowable (Art. 123 (2) EPC).

Dependent claims 2-12, 14-16 in so far as related to "pemetrexed" are consequently not allowable according to Art. 123(2) EPC.

2.21. The original document referred to by the EPO is the original PCT application WO 093, of which line 31 on page 1 and lines 1-9 on page 2 read as follows

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 ("DHFR") characteristic is Methotrexate®. An example of an antifolate that has glycaminide ribonucleotide formyltransferase inhibiting ("GARFT") characteristic is Lometrexol.

5 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 glycaminide ribonucleotide formyltransferase inhibition.

Lines 6-16 on page 6 read as follows

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycaminide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include 5-fluorouracil, as manufactured by Glaxo, Tomudex®, as manufactured by Zeneca, Methotrexate®, as manufactured by Lederle, Lometrexol®, as manufactured by Tularik, pyrido[2,3-d]pyrimidine derivatives described by Taylor et al. in U.S. Pat. Nos. 4684653, 4833145, 4902796, 4871743, and 4882,334, derivatives described by Akamatsu in U.S.

10 Pat. No. 4997838, thymidylate synthase inhibitors as found in EPO application 239,362, and most preferred, Pemetrexed Sodium (ALIMTA), as manufactured by Eli Lilly & Co.

2.22. By letter of 8 March 2006, Burnside filed the claims currently in force and informed the examiner of the following

I refer to the Communication pursuant to Article 96(2) EPC dated 17 May 2005 and enclose new pages 3, 4, 4a, 5, 6, 7, 8, 10, 11, 11a, 13, 14, 15 and 16 and new Claims 1-14 to replace pages 3-8, 10, 11 and 13-16 and Claims 1-16 presently on file.

Amendments

The Claims have been amended to refer to the preferred embodiment, the use of pemetrexed disodium (ALIMTA®) as manufactured by Lilly and Company, as the antifolate drug. The Claims have also been amended to incorporate the list of vitamin B12 derivatives set out on page 7 lines 6-7 of the application as filed.

(...)

The description has been amended in conformity with the new Claims. The passages on pages 3 and 4 have been edited. The Applicant seeks to draw a distinction between subject matter which is relevant to the invention which is indicated as being that to which "the present invention generally relates" and "the subject matter provided by the invention" which is the subject matter claimed. In particular it is highlighted that the reduction of toxicity of the anti-folate in the use of the combination therapy is relevant to the invention and should be retained.

(...)

For the Examiner's ease of reference I enclose a copy of previous description pages 3-8, 10, 11 and 13-16 showing the changes in manuscript.

2.23. The annex to the above-mentioned letter contains a copy of the description from the PCT application including the following handwritten changes implemented by Burnside (now: paragraph [0022] of EP 508):

X14173 EP

< The "antifolate" or "antifolate drug" for use in this invention is >

-6-

be administered in addition to the methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is

- 5 pretreated with the methylmalonic acid lowering agent, and then treated with folic acid, followed by treatment with the antifolate compound.

The terms "antifolate" and "antifolate drug" generally refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include 5-fluorouracil, as manufactured by Glaxo, Temozolomide, as manufactured by Zeneca; Methotrexate, as manufactured by Lederle; Lometrexol, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al. 10 in U.S. Pat. Nos. 4684653, 4833145, 4902796, 4871743, and 4882,334; derivatives described by Akimoto in U.S. Pat. No. 4997838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred Pemetrexed Sodium (ALIMTA), as manufactured by Eli Lilly & Co. 15

2.24. The Communication by the EPO of 4 October 2006 reads as follows

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

(...)

Comments

(...)

Page 5, lines 22, 28, 32; page 6, line 5; page 9, lines 4, 16, 30: introduction of "pemetrexed disodium" to adapt description to claims on file (Art. 84 EPC).

Page 4, lines 24 and 25, introduction of "disodium" after "pemetrexed" to adapt description to claims on file (Art. 84 EPC)

The examiner implemented the changes himself in the 'Druckexemplar' in handwritten form.

- 2.25 By letter of 2 February 2007, Burnside, on behalf of Lilly, announced that it accepts these changes to the specification.

I refer to the Communication under Rule 51(4) EPC dated 4 October 2006 and approve the text specified therein subject to a minor formal change to claim 11.

- 2.26 Lilly is also the holder of European patent EP 1 265 612 B1 (hereinafter: EP 612), which was granted on 26 May 2004 in response to an application to that end of 23 January 2001 for a '*Pharmaceutical composition comprising pemetrexed together with monothioglycerol, L-cysteine or thioglycolic acid*'. Paragraph [0020] of the specification of this patent states:

As used herein, the term "pemetrexed" refers to the stable salts, acids and free base forms thereof. The term includes, for example, the free acid, the pharmaceutically acceptable alkali metal, alkaline earth metal, non-toxic metal, ammonium, and substituted ammonium salts, such as for example, the sodium, potassium, lithium, calcium, magnesium, aluminium, zinc, ammonium, trimethylammonium, triethylammonium, monoethanolammonium, triethanolammonium, pyridinium and substituted pyridinium salts. The substituted ammonium salts are one especially preferred group of salts.

Burnside was also involved in the granting of this patent as Lilly's patent agent.

Fresenius and Pemetrexed Fresenius

- 2.27 Fresenius is part of the Fresenius group. It is active in the pharmaceutical market and markets several generic medicinal products for intravenous administration worldwide.
- 2.28 One of the products of the Fresenius group is "Pemetrexed Fresenius Kabi" (hereinafter: "Pemetrexed Fresenius Kabi"): Pemetrexed Fresenius) which is indicated for malignant mesothelioma of the pleura and not small cell lung carcinoma.
- 2.29 The SmPC of this generic product states that Fresenius is the representative of the marketing authorisation holder Fresenius Kabi Oncology Plc. in the Netherlands. The latter obtained the marketing authorisation by applying the centralised procedure within the meaning of EC Regulation 726/2004.¹ In this respect, Lilly's product Alimta® was referred to as a reference product.

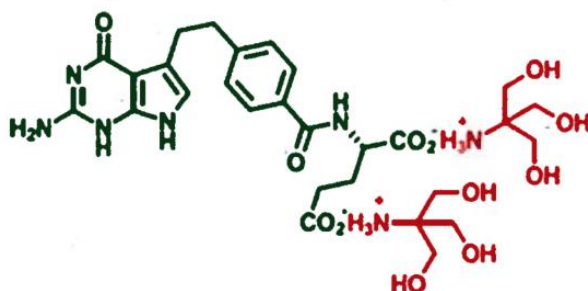
¹ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

- 2.30 Like Alimta®, Pemetrexed Fresenius has the pharmaceutical form of a (freeze-dried) powder for concentrate for solution for intravenous infusion. The same excipients that were used for Alimta® have also been used for this formulation, on the understanding that the excipient tromethamine is used instead of sodium hydroxide. The SmPC of Pemetrexed Fresenius includes the following under section 4.2 (dosage and method of administration):

To reduce toxicity, patients treated with pemetrexed should also receive vitamin supplements (see section 4.4). Patients should orally take folic acid or a multivitamin preparation with folic acid (350 to 1000 micrograms) on a daily basis. During the seven days prior to the first dose of pemetrexed, at least five doses of folic acid must be taken and this must be continued during the entire treatment period and for 21 days after the last dose of pemetrexed. Patients should also be given an intramuscular injection of vitamin B12 (1000 micrograms) in the week prior to the first dose of pemetrexed and thereafter once every three cycles. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

The SmPC also states that the medicinal product in powder form should be diluted in a glucose solution for infusion.

- 2.31 In Pemetrexed Fresenius, the two hydrogen atoms as found in pemetrexed diacid (see again 2.3) have been replaced by tromethamine groups (hereafter also: the pemetrexed tromethamine). The molecular structure of Pemetrexed Fresenius is shown below, marked in red are the tromethamine groups that are separated from the rest of the molecule as cations when mixed with an aqueous solution for infusion, after which the (green-coloured) pemetrexed anion remains.



- 2.32 The European Public Assessment Report for Pemetrexed Fresenius includes the following, among other things:

Page 7:

The difference in active substance salt form between the applied product and the reference product is therefore not relevant for the clinical efficacy and safety of the ready to use infusion.

Page 8:

The active substance in Fresenius Kabi's Pemetrexed for Injection is pemetrexed diacid instead of pemetrexed disodium as in the originator product Alimta. Both products are intended for intravenous use and must be reconstituted and further diluted prior to use. When reconstituted and diluted for administration, the active moiety remains the same irrespective of the salt form.

Page 11 :

The excipients used in the formulation of Pemetrexed Fresenius Kabi are the same used in the reference product except sodium hydroxide, which is replaced by trometamol. Trometamol is a known buffering agent/pH adjuster and solubilizer.

Page 12:

No bioequivalence study was deemed required as the finished product is to be administered as an aqueous

solution containing the same active substance in the same concentration as the reference product.

Page 16:

The active substance in Fresenius Kabi's Pemetrexed for Injection is Pemetrexed diacid instead of Pemetrexed disodium as in Alimta 100 mg/500 mg powder for concentrate for solution for infusion. When reconstituted and diluted for administration, the active moiety remains the same irrespective of the salt form. Accordingly, both medicinal products are considered to contain the same active substances.

Trometamol is a known buffering agent/pH adjuster used in formulations available in Europe and US. It is agreed that the quantity used in Fresenius Kabi's formulation is less than the required quantity to produce pharmacological action and would not be expected to cause any adverse effects of its own. The other excipients are well known and commonly used in aqueous intravenous solution available on the European market. The existing differences in the excipients of the applied product as compared to the reference product are not expected to have any significant impact in properties with regards to bioavailability, pharmacokinetics, safety and efficacy between these products.

- 2.33 Fresenius included its generic product in the doses of 100 mg and 500 mg in the G-standard of Z-index for February 2017, published on 17 January 2017.

Other proceedings

- 2.34 Various proceedings regarding infringement or (non-)infringement of EP 508 have been conducted in Europe between Lilly on the one side and Fresenius or other offerors of generic pemetrexed products on the other side, including the proceedings described below.

The Netherlands

- 2.35 In the Netherlands, the preliminary relief judge of the District Court in The Hague imposed an injunction on Sandoz B.V. by judgment of 1 March 2017, prohibiting it from marketing generic pemetrexed disodium (ECLI:NL:RBDHA:2017:1907). By judgments of 24 October 2017, the preliminary relief judge of the same district Court also imposed injunctions on Teva Nederland B.V. and Fresenius (ECLI:NL:RBDHA:2017:12045 and ECLI:NL:RBDHA:2017:12046). These judgments in preliminary relief proceedings were confirmed by this Court of Appeal by judgments of 8 May 2018 (ECLI:NL:GHDHA:2018:1106 and ECLI:NL:GHDHA:2018:1105). Fresenius lodged an appeal in cassation against the judgment rendered against it. The Court of Appeal is officially aware that the Supreme Court rejected the appeal in cassation by judgment of 12 June 2020 (ECLI:NL:HR:2020:1036).
- 2.36 Sandoz B.V. instituted invalidity proceedings with regard to EP 508 before the District Court in The Hague. A judgment was rendered in those proceedings on 16 January 2019 (ECLI:NL:RBDHA:2019:321) and the claims were rejected. Sandoz B.V. lodged an appeal against that judgment. This appeal had not yet been decided when this case was heard.

United Kingdom

- 2.37 In 2012, Actavis UK Limited et al. (now Teva) instituted non-infringement proceedings against Lilly before the High Court. It requested a judicial declaration that commercialisation of specific types of salt forms of pemetrexed (pemetrexed dipotassium, pemetrexed diacid and pemetrexed ditromethamine) does not infringe EP 508 in the United Kingdom, France, Italy and Spain. The High Court declared itself competent in respect of the French, Italian and Spanish patents. In its judgment of 15 May 2014, Justice Arnold (hereinafter: Arnold J) granted a declaration of non-infringement, in which he considered that the products mentioned by Actavis neither directly nor indirectly infringe EP 508.

- 2.38 On appeal, the Court of Appeal concurred with Arnold J's judgment in a judgment of 25 June 2015 (handed down by Lord Justice Floyd with agreement of Kitchin LJ and Longmore LJ) with regard to the opinion that there is no direct infringement. However, Arnold J's judgment was partially set aside with regard to the finding of indirect infringement. If the pemetrexed products mentioned by Actavis are diluted in a saline solution (with sodium chloride), the Court of Appeal believes this constitutes an indirect infringement of EP 508. The question whether there is also indirect infringement if the recommendation is to dilute the pemetrexed diacid or dipotassium salt in a dextrose solution was referred back to the High Court.
- 2.39 The UK Supreme Court (hereinafter: UKSC) held in a judgment dated 12 July 2017 (with a leading speech by Lord Justice Neuberger) that the scope of protection of EP 508 also extends to salts other than pemetrexed disodium, so that the pemetrexed products mentioned by Actavis directly infringe EP 508.

Germany

- 2.40 Lilly instituted preliminary relief proceedings against Fresenius Before the Landgericht Munich. By judgment of 29 November 2016, the Landgericht assumed infringement.
- 2.41 Lilly also initiated infringement proceedings against Actavis (now: Teva). In a judgment dated 3 April 2014, the Landgericht Düsseldorf held that pemetrexed dipotassium (of Actavis) as an equivalent directly infringes the German part of EP 508. On appeal, the Oberlandesgericht Düsseldorf held in a judgment dated 5 March 2015 that the scope of protection of EP 508 is limited to pemetrexed disodium, so that the use of pemetrexed dipotassium does not result in direct infringement – not on the basis of equivalence either. On appeal in cassation, the Bundesgerichtshof (hereinafter: BGH) referred the case back to the Oberlandesgericht Düsseldorf in a judgment dated 14 June 2016, because the BGH was of the opinion that the Oberlandesgericht Düsseldorf had not correctly applied the German doctrine of equivalence. Due to a settlement between the parties, there will be no judgment in the case referred back.
- 2.42 Lilly claimed an *ex parte* injunction vis-à-vis Ratiopharm (also part of the Teva group), which injunction was granted by the Landgericht München on 6 April 2016. On 24 June 2016, after an *inter partes* hearing, the Landgericht München upheld the provisional injunction, ruling that Ratiopharm's pemetrexed diacid directly infringes EP 508 as an equivalent. On appeal, the Oberlandesgericht München maintained the decision of the Landgericht München in a judgment dated 18 May 2017.
- 2.43 By judgment of 18 July 2018, the Bundespatentgericht declared the German part of EP 508 invalid further to the claim of Hexal, Strada and Ratiopharm. Lilly lodged an appeal against the judgment. At the time this case was being heard, no judgment had yet been rendered in that appeal.
- 2.44 By judgment of 3 April 2019, the Landgericht München lifted the injunction for infringement imposed on Fresenius and Zentiva Pharma. The Oberlandesgericht München maintained this decision on appeal.

Switzerland

- 2.45 In a judgment dated 9 March 2017, the Bundespatentgericht allowed the declaration of non-infringement for the pemetrexed products (dipotassium, ditromethamine or diacid) claimed by Actavis. On 20 October 2017, the Bundesgericht, the highest Swiss court, set aside the decision of the Bundespatentgericht on appeal and held that the Amtiris® product marketed by Actavis

(which is the same product as Armisarte®) infringes EP 508. The Bundesgericht referred the case back to the Bundespatentgericht to review whether the two products that Actavis has not marketed, pemetrexed dipotassium and pemetrexed ditromethamine as a freeze-dried product (which is the same product as that of Fresenius), infringe EP 508 as well. On 21 December 2017, the Bundespatentgericht ruled that these products also infringe EP 508.

- 2.46 Sandoz brought an invalidity claim against the Swiss part of EP 508. By judgment of 15 October 2019, the Bundespatentgericht ruled that EP 508 is valid and rejected the claim.

Denmark

- 2.47 *Al.* On 8 December 2017, the Danish Maritime and Commercial Court awarded the preliminary infringement injunction against Fresenius Kabi, claimed by Lilly. The Østre Landsret confirmed this judgment by decision of 20 December 2018.

Austria

- 2.48 After initially rejecting an *ex parte* injunction requested by Lilly, the Handelsgericht Wien imposed an injunction on Fresenius in *inter partes* proceedings on 22 December 2017. By decision of the Oberlandesgericht Wien of 12 April 2018, the infringement injunction was confirmed. Proceedings on the merits are pending between the parties before the Handelsgericht in Vienna.

Finland

- 2.49 On 29 December 2017, the Finnish court awarded an injunction against Actavis and Ratiopharm at Lilly's request.

Sweden

- 2.50 On 31 January 2018, the Tingsrätt Stockholm awarded Lilly's claim for an injunction against Actavis for infringement.
- 2.51 Lilly also instituted preliminary relief proceedings against Fresenius in Sweden. By judgment of 23 March 2018, the Tingsrätt Stockholm assumed infringement. Proceedings on the merits are pending between the parties before the same district court.

Italy

- 2.52 In the preliminary relief proceedings instituted by Fresenius against Lilly before the District Court in Milan to obtain a judicial declaration of non-infringement, the District Court ruled in a judgment of 10 September 2017 that Fresenius does not infringe EP 508 with its pemetrexed product. On appeal, the Tribunale di Milano ruled by judgment of 15 October 2018 that the generic Pemetrexed Fresenius infringes the Italian part of EP 508. Other proceedings on the merits are pending between the parties before the same tribunal.

Belgium

- 2.53 By judgment of 29 January 2019, the Brussels Court of Appeal set aside a judgment of the Commercial Court of 15 June 2018 rejecting an injunction for infringement sought by Lilly against Fresenius. The proceedings are still pending before the Court of Appeal.

Portugal

- 2.54 By judgment of 22 April 2019, the Arbitration Tribunal of Lisbon assumed infringement in a case brought by Lilly against Fresenius. Fresenius did not lodge an appeal against that judgment.

3. The dispute

3.1. At first instance, Lilly claimed – in summary – that the District Court, in a judgment enforceable regardless of any appeal, both by way of provisional relief and as an order in the main proceedings, impose an injunction against Fresenius banning infringement in the Netherlands and order Fresenius to cease and desist any unlawful act against Lilly, subject to a penalty, and furthermore a judicial declaration in the main proceedings to the effect that that Fresenius has infringed EP 508 in the Netherlands, with ancillary claims, including filing a statement, sending a letter of correction to its customers and publishing a correction on its website, and ordering Fresenius to pay compensation for the damage suffered by Lilly and surrender of profits, and ordering Fresenius to pay the full costs of the proceedings, plus statutory interest.

3.2. By judgment of 19 June 2019, the District Court rejected Lilly's claims on the ground that Pemetrexed Fresenius does not fall within the scope of protection of the patent. In the opinion of the District Court, the reasonable degree of legal certainty would not be sufficiently achieved if, despite the specific wording "pemetrexed disodium" in the claims and the specification and in the light of the prosecution history indicating that the wording is based on a deliberate choice, the patent were extended to cover all forms of the antifolate pemetrexed. According to the District Court, it also follows from this that there is no room for equivalent protection in this case.

3.3. On appeal, Lilly claims, after increasing its claim, that the Court of Appeal set aside the judgment of the District Court and, in a new judgment, allow Lilly's claims later on and order Fresenius to repay the full amount of Lilly's payment pursuant to the judgment, plus statutory interest, ordering Fresenius to pay the full costs of the proceedings in both instances in accordance with Article 1019h of the Dutch Code of Civil Procedure (hereinafter: DCCP) and stipulating that Fresenius must pay statutory interest on the legal costs as from two weeks of the date of the judgment. In addition, Lilly increased its claim on appeal by an alternative version of the claimed of the auditor's statement. Lilly puts forward eleven grounds for appeal, with which it intends to present the dispute to the Court of Appeal in its entirety. Fresenius challenges Lilly's ground for appeal and puts forward six cross-appeals.

4. Assessment of the case on appeal

- 4.1. The parties disagree on the scope of protection of the patent.

Article 69(1) of the European Patent Convention (hereinafter: EPC), which applies here on the basis of Article 2(2) EPC, provides the following in this respect:

The scope of protection of the European patent is determined by the claims. Nevertheless, the specification and drawings are used to interpret the claims.

The Protocol in Article 69 EPC on the interpretation of Article 69 of the Convention (hereinafter referred to as the Protocol), reads as follows:

- 1 . Article 69 should not be interpreted as meaning that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Nor should it be taken to mean that the claims serve only as a guideline and that the actual protection

conferred may extend to what, from a consideration of the description and drawings by a skilled person, the patent proprietor has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patent proprietor with a reasonable degree of legal certainty for third parties.

- 2 For the purpose of determining the scope of protection conferred by a European patent, due account shall be taken of any element which is equivalent to an element specified in the claims.

4.2. Under Article 31(1) of the Vienna Convention, a treaty must be interpreted in good faith in accordance with the ordinary meaning of the terms of the treaty in their context and in the light of the object and purpose of the treaty. It follows from Article 31(3), opening words and under (b) of the Vienna Convention that account shall be taken, together with the context, of any subsequent practice in the application of the treaty which establishes the agreement of the parties regarding its interpretation, which entails that the prevailing view in the case law and literature of the contracting parties also constitutes a primary means of interpretation of the treaty.

4.3. In case law and literature, the following two approaches can be distinguished in the way in which Article 69 EPC and the Protocol are interpreted and, more specifically, the way in which an element that is equivalent (hereinafter also referred to as "equivalent") to an element defined in the claims can be taken into account when determining the scope of protection:

4.3.1. The first approach establishes the scope of protection in two steps. The first step is to determine, on the basis of an interpretation of the patent claim, whether the product or process of a third party meets all the features of that patent claim. If the patent claim cannot be interpreted in such a way that all of its features are to be found in the product or process, a second step is to determine whether the element deviating from a feature included in the claim is equivalent to that feature and whether it is appropriate to include the product or process within the scope of protection of the patent for that reason.

4.3.2. In the second approach, the equivalence of elements of a product or process to features defined in the patent claims is already taken into account in the interpretation of the patent claims. This approach therefore leaves little or no room for a second step in which equivalence is tested separately.

4.4. Examples of both approaches described above can be found in Dutch case law. In other EPC member states, the two-step approach described under 4.3.1 is currently the prevailing view. A two-step approach is established case law in Germany and France, among other countries. In the United Kingdom, the one-step approach referred to at 4.3.2 was followed until recently, but in its judgment of 12 July 2017 in the *Actavis - Lilly* case, the British UKSC expressly opted for the two-step approach (see para. 2.39). In view of this, it must be assumed that the two-step approach is also currently the prevailing view in the United Kingdom. Now that the two-step approach prevails in other EPC member states and also has a basis in Dutch case law, the Court of Appeal will apply that approach hereafter.

4.5. The first step of the two-step approach is referred to as the assessment of "literal infringement". This does not mean the limit referred to in Article 1 of the Protocol, whereby the scope of protection of the European patent is strictly defined by the literal text of the claim, but an interpretation of the patent claims in the light, *inter alia*, of the description and drawings from the point of view of the average skilled person with his knowledge of the prior art (Article 69(1) EPC and the centre of Article 1 of the Protocol). This step does not take into account the possible equivalence of elements of the product or process to features of the patent claims in accordance with Article 2 of the Protocol.

4.6. The second step concerns the question whether, according to the perception of the average skilled

person, the claims, read in the light of the specification and the drawings, leave room for equivalents, in view of fair protection for the patent proprietor and a reasonable degree of legal certainty for third parties on the other.²

4.7. In order to be able to give a positive answer to the aforementioned equivalence question, it is first of all required that the deviating element is technically equivalent to the claimed feature. That requirement is met if the product or process with the deviating element also solves the problem that the patent solves and the deviating element fulfils the same function in that context as the claimed features. This requirement of "technical equivalence" forms the basis for the reliance on equivalence.

4.8. Secondly, it must be assessed whether, from the point of view of the fair protection of the patent proprietor, it is appropriate to take account of equivalents when determining the scope of protection of the patent. That point of view requires the scope of protection of the patent to be proportionate to the contribution that the patent proprietor has made to the prior art with the patent. In addition to the novelty and inventive step of the variant, which will be discussed separately below as a fourth requirement, this means that the invention must have been disclosed in the patent specification in such a way that it is obvious to the average skilled person to use that invention with elements which differ from the features of the patent claim. In other words, the patent specification must disclose to the average skilled person, with his or her common general knowledge, a teaching that may include the application of equivalents.

4.9. This requirement does not mean that every equivalent for the average skilled person must have sufficiency of disclosure on the priority or application date. In the context of the question of whether there is an equivalent element, importance can in fact also be attached to the knowledge of the average skilled person at the time of the infringement.³ In addition, when assessing the relationship between the scope of protection and the contribution to the prior art, account should be taken of the degree of innovation brought about by the patent, since a high degree of innovation may impede the applicant's ability to adequately foresee and describe all embodiments.⁴

4.10. Thirdly, it must be assessed whether recognition of the claim of equivalence is appropriate in a specific case in view of the required reasonable degree of legal certainty for third parties. The fact that the wording used in the patent claims does not literally include equivalents is an important circumstance in that context. Given that Article 69 of the EPC requires that the scope of protection of a European patent is determined by the claims, third parties may, in principle, rely on the text of the claims, interpreted in the light of the specification and drawings, and any lack of clarity created by the wording of the claims is, in principle, to the detriment of the patent proprietor. However, the patent claims contain wording that does not literally reflect those equivalents is not sufficient for the finding that legal certainty for third parties is insufficiently warranted. If that were the case, it would be impossible to rely on equivalence. Such an outcome would not be in accordance with Article 2 of the Protocol, which requires due account to be taken of equivalence. A reliance on equivalence should therefore be possible if, despite the specific wording of the claims, a sufficient degree of legal certainty is ensured. There is a sufficient degree of legal certainty if the average skilled person understands that the patent claims leave room for equivalents, because the teaching of the patent for the average skilled person is clearly broader than the wording of those claims and, in the average skilled person's view, there are no valid grounds for limiting the scope of protection to application of the feature mentioned in the claims. Such a valid ground does not exist only if the average skilled person can assume that part of the protection has been waived.

4.11. Fourthly, if the defence gives reason to do so, it must be assessed whether the variant is new and has inventive step in relation to the prior art of the patent. Granting protection for non-new or non-

² Supreme Court 5 February 2016, ECLI:NL:HR:2016:196, Bayer-Sandoz, para. 3.3.7.

³ Supreme Court 4 April 2014, ECLI:NL:HR:2014:816, *Medinol-Abbott*, para. 3.5.2.

⁴ Supreme Court 25 May 2012, ECLI:NL:HR:2012:BV3680, *Aga-Occlutech*, para. 4.2.6.

inventive products or processes would go beyond what would justify fair protection for the patent proprietor (also known from the Gillette or Formstein defence, named after two cases of the same name from England and Germany, respectively). These aspects should be assessed in the context of determining the scope of protection of the patent because the novelty and inventive step of equivalents are not assessed in granting, opposition and invalidity proceedings.

the average skilled person

4.12. In the following assessment of the scope of protection of EP 508, the Court of Appeal will assume that the average skilled person is a team consisting of an oncologist and a chemist with expertise in the formulation of pharmaceutical preparations. Lilly disputes the fact that a chemist is part of the team, but also assumes that the average skilled person has specialised pharmacological knowledge and is familiar with the search for and selection of suitable salts for a pharmaceutical preparation. A skilled person with that knowledge cannot be easily distinguished from the average skilled person described by the Court of Appeal. What is more, Lilly's own line of reasoning and the expert opinions submitted by Lilly also started from both oncologists and chemists.

no literal infringement

4.13. In so far as Lilly maintained its position that Fresenius is literally infringing the patent in appeal proceedings, that position must be rejected. Lilly itself has argued that the average skilled person understands that the term "pemetrexed disodium" refers to a specific salt form of pemetrexed, i.e. a derivative of pemetrexed diacid in which two hydrogen atoms have been replaced by two sodium atoms (among other things, notice of appeal, section 4.70). Lilly also did not, or at least not sufficiently, contest that the average skilled person will see the variant of pemetrexed that Fresenius uses in its product, namely pemetrexed diacid with tromethamine, as a different salt form from pemetrexed disodium. Lilly itself stressed that pemetrexed disodium and pemetrexed diacid with tromethamine are different salt forms (e.g. notice of appeal, section 4.73). Its experts, Frokjaer and Ostergaard, also state that it is clear to the average skilled person that Fresenius's product deviates from the "literal wording" of the patent claims in this respect (Exhibit 27 submitted by Lilly, section 6.9). In view of this, it must be concluded that the average skilled person will not equate pemetrexed diacid with tromethamine with the claimed feature "pemetrexed disodium", even if that feature is interpreted in the light of the description of the patent.

4.14. Lilly's argument that the average skilled person learns from the patent specification that the salt form of pemetrexed – in summary – is irrelevant to the inventive concept cannot lead to a different conclusion with regard to literal infringement. This argument is important for the assessment of the reliance on equivalence, but cannot, in this case, lead to a broader interpretation of a term in the patent claims which has a more limited meaning in the context of both common general knowledge and patent law.

Question 1: Technical equivalence

4.15. The problem that EP 508 intends to solve, as the patent specification makes clear in, inter alia, paragraphs [0003] through [0005] and [0016] of the description, is to reduce certain adverse reactions of antifolates, such as pemetrexed disodium, while maintaining the therapeutic efficacy of the antifolate. The patent teaches that this problem can be solved by combining the antifolate with vitamin B12 and, optionally, folic acid.

4.16. Partly in view of the above description of the problem and its solution, the average skilled person will not deduce from the fact that the invention has been claimed as application of pemetrexed disodium in "the preparation of a medicinal product" that the contribution of the claimed invention lies in a specific method of preparation. The average skilled person will realise that this method of claiming has a purely

patent-law background, which is related to the fact that Article 53, opening words and under c EPC excludes medical treatment methods as such from patenting.

4.17. It has been established, as insufficiently contested, that both the therapeutic efficacy that the patent aims to preserve and the adverse reactions that the patent aims to reduce are caused by the pemetrexed anions and that the salt form claimed does not affect that therapeutic efficacy and adverse reactions of the pemetrexed anions or the toxicity reducing properties of vitamin B12 when administered in combination with pemetrexed disodium (and optionally folic acid). Lilly substantiated this statement with a publication by Sierra and Goldman on the transport of folates and antifolates in the cell (Exhibit 29 submitted by Lilly) and expert statements by an oncologist (statement by Professor Smit, Exhibit 26 submitted by Lilly) and chemists (statement by Professor Frokjaer and Professor Ostergaard, Exhibit 27 submitted by Lilly). Fresenius has merely argued that the properties of salts differ and that a salt form *could* affect their efficacy and toxicity. However, it has not contested that the salt form in the case of pemetrexed disodium has no effect on efficacy and toxicity.

4.18. In the light of the foregoing, as Lilly argued, the function of the salt form pemetrexed disodium in the light of the invention described above is solely to provide the pemetrexed anions. More specifically, Lilly argued, uncontested as such, that the salt form in this context has three relevant properties:

4.18.1. Firstly, Lilly explained that the salt form ensures that the negatively charged pemetrexed anions are available in a neutral substance that is sufficiently stable to be stored and traded (see also para. 2.10).

4.18.2. Secondly, Lilly argued that the salt form ensures that in an aqueous solution the pemetrexed anions dissociate from the sodium ions and thus become freely available.

4.18.3. Thirdly, Lilly noted that the salt form is pharmaceutically acceptable (also otherwise), i.e. suitable for use as a medicinal product.

4.19. It is established, as not or at least insufficiently contested, that the use of Pemetrexed Fresenius in combination with vitamin B12 and optionally folic acid in the treatment of lung cancer achieves the above described effects and benefits of the invention claimed in EP 508, i.e. fewer adverse reactions while maintaining therapeutic efficacy. It is also established that the form in which Fresenius markets its product, i.e. pemetrexed diacid with tromethamine, fulfils the same function as pemetrexed disodium in that respect, namely merely to provide pemetrexed anions. It is not in dispute that the counter ions in Pemetrexed Fresenius, i.e. the hydrogen particles and the tromethamine groups, also bind to the pemetrexed anions and thus form a substance that is sufficiently stable to be stored. It is also not in dispute that pemetrexed anions are made freely available in liquid, because pemetrexed diacid with tromethamine dissolves therein and the hydrogen particles and tromethamine groups dissociate from the pemetrexed anions. Nor is it in dispute that pemetrexed is pharmaceutically acceptable in this form, too. Fresenius has not disputed that the difference in salt form does not affect the efficacy and safety of the medicinal product. Lilly argued this with reference to the documents submitted by Fresenius in the context of the application for a marketing authorisation, comparing the products of Lilly and Fresenius and, inter alia, explicitly stating that *"the difference in active substance salt form between applied product and the reference product is [...] not relevant for the clinical efficacy and safety of the ready to use infusion"* (Exhibit 8 submitted by Lilly) (see also para. 2.32 above). In these proceedings, Fresenius also explicitly acknowledges that there is biologic equivalence (Defence on Appeal also Statement of Appeal in the cross-appeal, paragraph 3(e)).

4.20. Fresenius's argument that the bioequivalence to which its documentation refers cannot be equated with technical equivalence in the sense of patent law must be disregarded. The properties of the salt form pemetrexed disodium which determine the bioequivalence of the pemetrexed compounds, in particular

their therapeutic efficacy and safety, are in this case also relevant in the context of the assessment of technical equivalence because they have a function in the context of the invention. Contrary to what Fresenius asserts, there is equivalence not only "at the level of the biological effect after administration in the patient", but also "at the level of the pharmaceutical preparation". As considered above, the function of the sodium ions in the preparation is to neutralise the pemetrexed anions so that they can be stored and traded. It is not in dispute that the hydrogen particles and tromethamine groups fulfil the same function in the product marketed by Fresenius.

4.21. Fresenius' reasoning that the properties of salts are very different and that not all salt forms are a suitable alternative to pemetrexed disodium can be disregarded. For the assessment of the reliance on equivalence, not all properties of all pemetrexed compounds are relevant, nor is it necessary to establish that all pemetrexed compounds are a suitable alternative to pemetrexed disodium. It is sufficient that Pemetrexed Fresenius fulfils the same function as pemetrexed disodium in the context of the claimed invention. Fresenius also did not indicate that pemetrexed disodium has properties relevant to the invention that Pemetrexed Fresenius does not have. Fresenius did state that sodium salts have good solubility and that solubility is relevant to efficacy, but Lilly did not dispute that tromethamine is also known as a salt with high solubility. In view of this, it must be concluded that, in this respect too, Fresenius' product does not differ from the salt form mentioned in the patent claims.

Question 2: reasonable protection

4.22. Allowing the reliance on equivalence in this case is appropriate in the light of reasonable protection for the patentee and does not mean that the scope of protection of EP 508 goes beyond the contribution of the patent to the prior art. The invention is disclosed in the patent specification in such a way that the average skilled person could and would apply it with pemetrexed compounds other than the claimed pemetrexed disodium.

4.23. In this respect, it is important to note that the average skilled person would already arrive at the application of other pemetrexed compounds on the basis of his common general knowledge. It has been established, as not or at least insufficiently contested, that the average skilled person would come to realise on the basis of his common general knowledge that the function of pemetrexed disodium in the context of the claimed invention is merely to provide a substance which, in solution, produces pemetrexed anions and that the problem of reducing the side-effects of the pemetrexed anions without compromising the therapeutic efficacy of the pemetrexed anions could therefore also be solved with other pemetrexed compounds by administering vitamin B12 and, optionally, folic acid. In addition, Lilly argued –with reference to, among other things, the material patent for pemetrexed and as such without dispute – that the average skilled person was aware, on the basis of his common general knowledge, that other salts of pemetrexed could be produced with the same function as that of pemetrexed disodium. It is also not in dispute that the selection of suitable salt forms is a routine task for the average skilled person in the context of formulating a medicinal product. Lilly argued this with reference to statements made by experts in foreign proceedings and Fresenius did not contest this, or at least not with sufficient substantiation. It must therefore be assumed that the average skilled person could routinely determine whether an alternative pemetrexed compound fulfils the same function as that of pemetrexed disodium in the context of the invention.

4.24. Moreover, in addition to the specific teaching to apply pemetrexed disodium, the patent specification discloses much broader teachings that pertain to the application of alternative pemetrexed compounds. For instance, the patent specification explicitly teaches the skilled person that the invention relates to *"the discovery that administration of a methylmalonic acid lowering agent such as vitamin B 12 or a pharmaceutical derivative thereof, in combination with an antifolate drug such as pemetrexed disodium reduces the toxicity of the said antifolate drug"* (paragraph [0016] of the patent specification). This paragraph teaches the average skilled person, among other things, that the intended effect of

reducing side-effects while maintaining efficacy is not limited to a specific antifolate, let alone to a specific salt form of a specific antifolate. The text of the patent specification therefore also puts the average skilled person on track towards looking for alternatives to pemetrexed disodium. As considered above, the average skilled person would routinely arrive at alternative pemetrexed compounds that function in the same way.

4.25. Fresenius' argument that the average skilled person cannot predict the properties of a salt or acid prior to routine experimental research, does not lead to a different outcome. As both parties have pointed out with reference to the judgment rendered by the British High Court in the pemetrexed case,⁵ this unpredictability does not prevent the average skilled person from having a reasonable expectation of finding an alternative salt suitable for use in the context of the patented invention. The unpredictability of the properties of salts and acids would therefore not prevent the average skilled person from looking for an alternative pemetrexed compound.

4.26. In this context, it need not be discussed whether finding a suitable alternative is "childishly simple" as assumed by the District Court, but challenged by Fresenius. The fact that finding an alternative is within the average skilled person's reach contributes to the opinion that the scope of protection of EP 508 does not go beyond the contribution of the patent to the prior art. The fact that finding a suitable alternative pemetrexed compound was and is within the average skilled person's reach follows satisfactorily from the exhibits submitted by Lilly and has not been contested by Fresenius.

4.27. Fresenius' reasoning that it obtained a patent for the development of its formulation cannot lead to a different outcome. The fact that a product contains a measure which has inventive step in relation to the patent specification does not preclude that the teachings of the patent are also applied in that product and that it is therefore fair towards the patent proprietor to bring the relevant product within the scope of protection of the patent. Indeed, the inventive step may lie in a complementary teaching, in the form of the addition of a measure to the patented product or the selection of a specific embodiment of the general teachings of the patent. That situation also occurs in the present case. Lilly noted, undisputed, (i) that Fresenius's patent does not concern pemetrexed diacid with tromethamine as such, but pemetrexed diacid with tromethamine in a particular weight ratio in which the solvent is rinsed with an inert gas before, during or after mixing; and (ii) that the EPO indicated during the granting procedure that pemetrexed diacid with tromethamine as such was appropriate. This opinion of the EPO is supported by the fact that tromethamine, as Lilly substantiated and argued without dispute, was a commonly known buffering agent/H-regulator which was one of the top 10 most commonly used excipients.

question 3: reasonable legal certainty

4.28. In the opinion of the Court of Appeal, a reasonable degree of legal certainty for third parties is also ensured in this case. When interpreting the claims in the light of the specification, it will be clear to the average skilled person that the claims leave room for equivalents as far as the salt form is concerned. He will recognise that the teaching of the patent is clearly broader on this point than the wording of those claims and that there are no valid grounds for limiting the scope of protection to the application of the pemetrexed disodium mentioned in the claims.

4.29. As considered above, the patent specification explicitly discloses a teaching that includes the application of alternative pemetrexed compounds, namely that the adverse reactions of an antifolate can be reduced by administration in combination with vitamin B12 (and optionally folic acid). Moreover, that teaching is consistent with the knowledge with which the average skilled person reads the patent specification, including the knowledge that the pemetrexed anions are responsible for therapeutic efficacy

⁵ High Court 15 May 2014, [2014] EWHC 1511 (Pat) (Actavis/Lilly).

and adverse reactions and that the function of pemetrexed disodium in the context of the invention is merely to provide those pemetrexed anions after solution. For the average skilled person who interprets the patent with his common general knowledge, the teaching of the patent is thus clearly broader than the wording "pemetrexed disodium" of the claims. In other words, it is clear to the average skilled person that he uses the inventive concept behind the words of the claim by using alternative pemetrexed compounds.

4.30. It is also clear to the average skilled person that there are no valid grounds for limiting the scope of protection to application of the pemetrexed disodium mentioned in the claims. As will be explained below, the average skilled person will not find valid grounds for limiting the scope of protection in the patent specification, in the common general knowledge with which the average skilled person interprets the patent specification or in the prosecution history of the patent, even if those sources are considered in their interrelationship.

4.31. The patent specification does not mention a valid ground for limiting the scope of protection to the application of pemetrexed disodium. The patent specification does not mention any advantage of the salt form pemetrexed disodium over other pemetrexed compounds, nor does it describe any effect of that salt form, such as its "stability, solubility or absorption". The only thing the patent specification teaches on pemetrexed disodium is that Lilly produces pemetrexed in that salt form, i.e. that pemetrexed disodium is available. The average skilled person will not consider the fact that pemetrexed disodium is an existing product to be a valid ground for limiting the scope of protection of the patent to pemetrexed disodium. After all, on the basis of his common general knowledge, the average skilled person knows that and how other salts of pemetrexed could be developed that will have the same effect.

4.32. Contrary to what Fresenius believes, the fact that the patent specification in the claims and description exclusively mentions pemetrexed disodium, without adding a clause such as "or *other pharmaceutically acceptable salts*", does not constitute a valid ground for limiting the scope of protection of pemetrexed disodium. A reliance on equivalence would become impossible if that mere fact would constitute a valid ground for limiting the scope of protection to a product with that feature. That result would run counter to the rule that equivalents must be taken into account in an appropriate manner.

4.33. The fact that, the patent specification does explicitly mention alternatives for other features in the claims and the description, such as with vitamin B12 "*pharmaceutical derivatives thereof*", does not constitute a valid ground for limiting the scope of protection. It cannot be inferred from this fact *a contrario* that pemetrexed disodium equivalents are excluded from the scope of protection.

4.34. Finally, Fresenius referred to paragraph [[0016] of the specification, which states that the invention relates to "the discovery that administration of a methylmalonic acid lowering agent such as vitamin B 12 or a pharmaceutical derivative thereof, in combination with an antifolate drug such as pemetrexed disodium reduces the toxicity of the said antifolate drug". That passage does not provide valid grounds for limiting the scope of protection either. On the contrary, this passage, among others, explicitly teaches the skilled person that the invention is not limited to pemetrexed disodium (see 4.24 above).

4.35. A valid ground for limiting the scope of protection of EP 508 to the application of pemetrexed disodium also does not follow from the common general knowledge with which the average skilled person interprets the patent specification. On the contrary, as considered above, the common general knowledge teaches that the claimed invention is more broadly applicable with regard to the salt form.

4.36. Fresenius did rightly point out that the average skilled person knows on the basis of his common general knowledge that the salt form is "relevant" to the invention, in the sense that not every salt or acid of pemetrexed disodium can fulfil the functions of pemetrexed disodium in the context of an invention. It is conceivable, for example, that the solubility of a particular salt is so low that the salt will provide little or no free pemetrexed anions in a liquid and will therefore not be able to fulfil the functions that

pemetrexed disodium has in the context of the invention. However, this does not imply that there is good reason to exclude from the scope of protection of EP 508 the use of alternative pemetrexed compounds which do fulfil the same functions in the context of the invention, such as pemetrexed diacid with tromethamine.

4.37. The average skilled person will also know on the basis of his common general knowledge that the selection of an alternative pemetrexed compound requires research, the results of which cannot be predicted in advance. However, that expert also knows how to carry out that research and that he has a reasonable chance of success that he will find a suitable alternative with that research. Therefore, the need for that research does not provide valid grounds for limiting the scope of protection of the claims to pemetrexed disodium.

4.38. The fact that Lilly expresses its preference for pemetrexed disodium in the material patent (EP 0 432 677) and for pemetrexed disodium in another patent (EP 1 259 513 BI) for a heptahydrate form of pemetrexed disodium cannot lead to a different opinion. It has neither been argued nor proven that the beneficial properties that Lilly attributed to (a specific form of) pemetrexed disodium in the context of those patents were part of common general knowledge. In addition, Fresenius did not argue that the average skilled person believes that pemetrexed compounds without those properties could not fulfil the function that pemetrexed disodium has in the context of the invention. Fresenius did not sufficiently explain why the average skilled person would see a valid ground for limiting the scope of protection to pemetrexed disodium in these properties of pemetrexed disodium, whether or not a specific form thereof.

4.39. The fact that Lilly expressly disclosed and claimed other acids and salts in another patent (EP 1 265 612 BI) cannot lead to a different interpretation either. It cannot be concluded from this *a contrario* that the scope of protection of EP 508 must be limited to pemetrexed disodium.

4.40. In view of the foregoing, it must be concluded that it will be clear to the average skilled person from interpreting the patent claims in the light of the description that the claims of EP 508 in respect of the salt form also extend to equivalents. He does not need to study the prosecution history for this. If the average skilled person were to consult the prosecution history, he would not arrive at a different opinion, because no valid ground for limiting the scope of protection to the application of pemetrexed disodium can be found in the prosecution history either. On the contrary, as will be explained below, examination of the prosecution history would strengthen the average skilled person's opinion that the scope of protection is not limited to the application of pemetrexed disodium.

4.41. As Fresenius itself has also pointed out, the use of the feature pemetrexed disodium can be traced back to the original application, in which pemetrexed disodium as the only described form of pemetrexed (see para. 2.21 above). A valid ground for limiting the scope of protection to that salt form cannot be derived therefrom. The claims of the original application were in fact much broader and comprise –in summary –the application of *each* antifolate in combination with *methylmalonic acid lowering agent* (such as vitamin B12). The claims also comprise other pemetrexed disodium compounds than pemetrexed disodium.

4.42. The average skilled person will not see any good ground for limiting the scope of protection to the application of pemetrexed disodium in the further course of events during the granting procedure either. The prosecution history in fact confirms that Lilly envisaged a broader scope of protection which also comprises the application of other salts and acids of pemetrexed. Indeed, after the EPO's Examining Division argued that the broad claim was not novel in the light of two publications on the use of vitamin B12 in combination with antifolates other than pemetrexed, Lilly put forward a claim pertaining to –in summary – the application of "pemetrexed" in combination with vitamin B12 (see above at 2.17, 2.18 and 2.19). This claim, too, comprises other pemetrexed disodium compounds than pemetrexed disodium.

4.43. Examination of the prosecution history teaches the skilled person that the feature pemetrexed disodium was subsequently introduced following an objection by the Examining Division of the European Patent Office based on Article 123(2) of the EPC against the concept of 'pemetrexed' (see at 2.20). A limitation of the claims on that ground does not exclude a reliance on equivalence. It can only be deduced from that limitation that Lilly wished to ensure that the subject matter of its patent was covered by the content of the original application. A valid ground for limiting the scope of protection to the application of pemetrexed disodium, and the exclusion of equivalents, cannot be found there. This is because if reliance on equivalence within the context of the scope of protection is to succeed, there is no need for the equivalents to be covered by the contents of the original application. The rule from Article 123(2) EPC, as also acknowledged by Fresenius (Statement of Defence, para. 84 and Defence on Appeal, para. 167), does not apply when determining a patent's scope of protection. A distinction must be made between added matter and scope of protection.

4.44. Fresenius' reliance on the rationale of Article 123(2) EPC cannot lead to any other opinion. Fresenius argued that this provision protects the legal certainty of third parties, and ensures that the scope of the patent is reasonably proportionate to the patent proprietor's contribution to the prior art. It follows from the foregoing that those two aspects are also taken into account when assessing the reliance on equivalence. Application of Article 123(2) EPC by analogy is not necessary to that end.

4.45. There are also well-founded reasons not to apply the requirements of Article 123(2) EPC in the assessment of any reliance on equivalency within the context of determining the scope of protection of a patent. Specifically, there are essential differences between the addition of equivalents to the patent claims and the description on the one hand, to which Article 123(2) EPC applies, and on the other hand taking equivalents into account within the context of determining the scope of protection of the patent, to which Article 69 EPC and the Protocol pertain.

4.45.1. Firstly, adding equivalents to the patent claims and the description has a greater impact on the scope of protection. This is because the patent's scope of protection is determined by the claims in light of the description as they read after adding the equivalents. Under certain conditions, after this change that scope of protection can also cover equivalents of the added equivalents. That possibility does not occur when equivalents are invoked. That reliance may bring equivalents under the scope of protection under certain circumstances, but not equivalents of equivalents.

4.45.2. Secondly, the addition of an equivalent by way of amending the patent specification may impact the novelty, inventive step and sufficiency of disclosure of the patent, in the sense that the patent derives its novelty, inventive step and sufficiency of disclosure from the added equivalent, in full or in part. This would enable the applicant to create and obtain an unjustified advantage, as novelty, inventive step and sufficiency of disclosure are assessed on the application date, while on that date the equivalent was not part of the invention disclosed in the original application. This effect does not occur when equivalence is relied on in determining the scope of protection, as equivalents are not considered when assessing novelty and inventive step, and cannot repair any insufficient disclosure.

Because of these differences, Article 123(2) EPC imposes relatively strict requirements on the addition of subject matter to the patent specification that is not applied (by analogy) in determining the patent's scope of protection.

4.46. The circumstances put forward by Fresenius, for example that Lilly did not dispute the EPO regarding the objection based on Article 123(2) EPC, that Lilly is a pharmaceutical superpower that put much thought into opting for the limitation to the application of pemetrexed disodium, that Lilly did not apply for any divisional and that Lilly could have worded the patent's claims differently, cannot lead to a

different opinion here. Those circumstances do not change the fact that the average skilled person will conclude from the prosecution history that Lilly added the words "pemetrexed disodium" further to the added subject matter objection, and that from this the average skilled person will not derive any cause for the limitation of the scope of protection to the application of pemetrexed disodium.

4.47. The foregoing could be different if the average skilled person were to assume that added subject matter was not a real problem, and therefore that there must have been another reason for introducing the words pemetrexed disodium in the claims. Fresenius did not assert this; rightly so. Fresenius is not asserting that there would have been no added subject matter if Lilly had proposed a claim that included other pemetrexed compounds, let alone that the average skilled person would have understood this. Fresenius has merely asserted that Lilly had a reasonable chance of successfully parrying the Examining Division's objection. That is not sufficient for assuming that the average skilled person would think that there was another reason for introducing the wording, let alone that this gives cause to limit the scope of application.

4.48. Fresenius' argument that the average skilled person would conclude from the patent specification and the prosecution history that the use of the term "pemetrexed disodium" in the claims and the description was a deliberate choice, or a choice that was not clearly unintended by Lilly, cannot lead to any other opinion. In so far as Fresenius was thus referring to Lilly's subjective intention or intent, the argument can be disregarded because the subjective intention or intent of the applicant plays no decisive role in determining the patent's scope of protection. In so far as Fresenius is referring to what the average skilled person would conclude from the patent and the prosecution history in an objective sense, the argument coincides with the defence against Lilly's assertion that there is no good cause for limiting the scope of protection to the application of pemetrexed disodium. That defence was already rejected above.

4.49. In addition, the average skilled person will determine based on the prosecution history that the use of the term "pemetrexed disodium" in the claims originates from the clumsy wording of the application, in which Lilly laid no or at least no clear basis for a claim that is somewhere between one that is worded too broadly in light of the prior art when it includes all antifolates on the one hand, and on the other hand a claim that is worded too narrowly in light of the patent's contribution to the prior art when it exclusively refers to pemetrexed disodium. The wording of the original application cannot be considered a deliberate or not clearly unintended choice by Lilly to limit the scope of protection to the application of pemetrexed disodium. On the contrary: it is evident to the average skilled person that the wording was *not* intended to limit the scope of protection. For the average skilled person who finds the background behind the use of the term pemetrexed disodium in the claims of the patent as granted in the prosecution history, it is clear that Lilly never chose to limit the scope of protection to the application of pemetrexed disodium.

4.50. In so far as Fresenius intended to argue that the legal certainty of third parties must always prevail when careful wording of the original application and the patent specification *could* have been used to expressly claim an equivalent, that argument must be rejected. In general, that approach is taking things too far and fails to appreciate that when determining the scope of a patent's protection, account must be taken of reasonable legal certainty for third parties and fair protection of the patent proprietor.

4.51. The District Court's opinion that Lilly did not assert the existence of any unintended error or omission in the original application, that Lilly itself is of the opinion that the original application does offer a basis for a broader claim, and that Lilly did not assert that the average skilled person will understand that there is no basis for the broader claim, must be rejected. In any event on appeal, Lilly explicitly took the position that the original application does not offer any basis for broader claims, that the average skilled person will understand this, and – with hindsight – that it would have been better if the original application had said "pemetrexed and pharmaceutically acceptable salts thereof".

4.52. The fact that Lilly designated pemetrexed disodium in the patent application as the most

preferred embodiment does not give good cause to limit the scope of protection to pemetrexed disodium. That application mentioned no pemetrexed compounds other than pemetrexed disodium: it exclusively mentioned other antifolates. The average skilled person will not conclude from the fact that the application of pemetrexed disodium is to be preferred over other antifolates such as methotrexate and lomertrexol that pemetrexed disodium also has advantages over other pemetrexed compounds.

4.53. Lastly, Fresenius pointed out that Lilly's patent agent reported to the Examining Division in its letter of 8 March 2006 that Lilly "seeks to draw a distinction between subject matter which is relevant to the invention which is indicated as being that to which 'the present invention generally relates' and 'the subject matter provided by the invention' which is the subject matter claimed". In that comment, the average skilled person will find no good cause to limit the scope of protection to the application of pemetrexed disodium to the exclusion of other pemetrexed compounds. This is because the average skilled person studying the prosecution history will understand that the distinction to which the patent agent was referring was not introduced within the change in the claims from pemetrexed to pemetrexed disodium. That distinction was already part of the modified description that Lilly submitted by letter of 23 December 2004 within the context of changing the claims from all antifolates to pemetrexed. In that light, it must be assumed that the distinction pertains to the application of antifolates in general vs. the application of the antifolate pemetrexed. The reason why the patent agent drew attention to the distinction in the letter of 8 March 2006, as explained in that letter, was that the excerpts about "subject matter to which the present invention generally relates" were to be maintained in the description in order to make it clear that the diminished toxicity of the antifolate in the use of the combination therapy is relevant to the invention. The average skilled person will not conclude from this that the scope of protection is limited to pemetrexed disodium, to the exclusion of other pemetrexed compounds.

question 4: novelty and inventive step

4.54. Apart from the validity defence discussed below, Fresenius has not disputed that its product has novelty and inventive step as compared to the patent's prior art as referred to in para. 4.11 of this judgment. The Court of Appeal can depart from that premise for that reason.

conclusion scope of protection

4.55. Based on the foregoing, it must be concluded that Lilly's ground for appeal against the District Court's opinion that it adequately took account of alternatives is successful. Adjudicating again, the opinion must be that Fresenius' product falls under the scope of protection of at least claim 2 of EP 508. Lilly's other grounds for appeal in the principal appeal and the grounds of appeal put forward by Fresenius in the cross-appeal against the District Court's assessment of the scope of protection were considered in the previous assessment by the Court of Appeal and require no further discussion.

4.56. The opinion of the Court of Appeal regarding the scope of protection of EP 508 is in accord with the decisions of the highest foreign courts regarding the scope of protection of the foreign parts of EP 508. The Court of Appeal therefore does not need to explain how its opinion relates to those decisions.

4.57. This brings the Court of Appeal to the assessment of Fresenius' ground for appeal 6 in the cross-appeal regarding the validity of claims including claim 2 of EP 508, put forward by Fresenius in the event that the Court of Appeal finds that its product falls under the scope of protection of EP 508.

validity of claim 2

4.58. Fresenius' argument that for the person skilled in the art, the invention claimed in claim 2 of EP 508 ensues from the prior art in an obvious manner must be rejected for the following reasons.

4.59. Fresenius argued that the invention claimed lacks inventive step because:

- a. using antifolates, including pemetrexed disodium, in combination with folic acid to reduce the toxicity of the antifolate without detracting from the effectiveness of the antifolate was common general knowledge;
- b. it was also common general knowledge that a relationship existed between folate and vitamin B12 in the metabolism of a cell, and more in particular that by using vitamin B12 the folate trapped in the "folate trap" can be released and made available as a functional folate;
- c. for that reason alone, it was obvious for the skilled person to try – with a reasonable expectation of success – whether a shortage of functional folate could be resolved by administering vitamin B12;
- d. the step to vitamin B12 is all the more obvious as it was known that cancer patients, who are often already elderly, often have a vitamin B12 deficiency;
- e. otherwise there was no prejudice whatsoever against the use of vitamin B12 in the treatment of cancer.

Each of these assertions will be discussed in the same sequence below. Also in view of what was held above regarding the limited importance of the salt form, for the sake of brevity pemetrexed disodium will be referred to as pemetrexed.

Use of antifolates in combination with folic acid

4.60. Fresenius' assertion that using antifolates, including pemetrexed, in combination with folic acid to reduce the toxicity of the antifolate without detracting from the effectiveness of the antifolate, was common general knowledge must be rejected.

4.61. Lilly contested this by arguing that based on their common general knowledge, the average skilled person precisely would *not* combine antifolates with folic acid, as they would expect the administration of folic acid to undermine the effect of the antifolate. Lilly also pointed out that the average skilled person would realise on the basis of their common general knowledge that antifolates and folic acid (a synthetic folate) oppose one another's effectiveness because they compete with one another. Lilly substantiated this with expert statements (O'Dwyer's statement, Exhibit 60 submitted by Lilly, and Chabner's statement, Exhibit 71 submitted by Lilly) and a handbook for clinicians which reports that folic acid can impair the effectiveness of methotrexate – one of the two antifolates on the market in Europe (Exhibits 68-70 submitted by Lilly) – while the SmPC of the antifolate raltitrexed – the other antifolate on the market in Europe – explicitly says that folic acid must not be administered in combination with the antifolate because it may affect its effectiveness (Exhibit 58.4 submitted by Lilly).

4.62. As such, it is not in dispute that the average skilled person knew that antifolates and folic acid compete with one another. Fresenius itself argued that antifolates and folates administered via folic acid can both bind to enzymes that play a part in the division of cells, and that if the antifolate binds to the enzyme, it blocks the binding of the folate and thus prevents the enzyme from completing its work in the cell division process. It did not dispute that this is part of the common general knowledge of the average skilled person.

4.63. Nor did Fresenius substantiate its assertion using examples from combination therapies comprising an antifolate with folic acid that were used in clinical practice to treat cancer on the priority date. On the contrary: it has been established, as not or at least insufficiently contested, that such combination therapies were not used on the priority date. During oral arguments, Fresenius did point out a patent application by Vesta (Exhibit 52 submitted by Fresenius) and a publication by Carrasco (Exhibit 51 submitted by Fresenius). However, these documents do not disclose any combination therapy using an antifolate and folic acid to treat cancer. Those documents describe the administration of folic acid and other substances to treat an increased homocysteine level and its consequences, and acute megaloblastic anaemia (a special type of anaemia), respectively. The fact that the publications also mention that these may also present as symptoms as a result of the earlier administration of the antifolate methotrexate does

not mean that they disclose a combination treatment within the meaning of the Patent, let alone that they disclose that the combination of folic acid does not detract from the effectiveness of the antifolate.

4.64. Nor has Fresenius substantiated its assertions with publications about clinical research into the combination of antifolates with folic acid. Fresenius did point out publications about clinical phase I research into the combination of folic acid and antifolates such as pemetrexed (two abstracts by Hammond, Exhibits 39 and 40 submitted by Fresenius). However, Fresenius itself emphasised that this research does not lead to concluding anything regarding the effectiveness of the antifolate, because clinical phase I research focuses on determining the safety, maximum dosage and pharmacokinetics of the substance, rather than the effectiveness, and because the small number of participants in the research had already undergone many other treatments. The results of that research therefore cannot serve to substantiate Fresenius' assertion that it was common general knowledge that the administration of folic acid will not detract from the effectiveness of an antifolate.

4.65. Fresenius has primarily based its assertion in various publications in which the results of pre-clinical research into the administration of a combination of pemetrexed and folic acid in mice is described (Jackman, Exhibit 32 submitted by Fresenius, and the abstract and article by Worzalla, Exhibits 37 and 38 submitted by Fresenius, and by Cripps, Exhibit 35 submitted by Fresenius). However, results from preclinical research are insufficient to support Fresenius' assertion that it was common general knowledge to use antifolates in combination with folic acid without detracting from the effectiveness of the antifolate, certainly in light of the aforementioned knowledge of the average skilled person regarding the competitiveness between antifolates and folic acid. It may be common general knowledge that the results from preclinical research "suggest" favourable effects from the administration of folic acid, as phrased by Jackman, cited by Fresenius, but that is not the same as it being common general knowledge that those effects exist.

4.66. What is more, the published preclinical research results make it clear that when administering folic acid, pemetrexed must be administered to mice in much higher doses to achieve the same effect. The publications teach that with mice to which no folic acid is administered, tumour growth is already completely inhibited with a dose of 0.3 mg/kg. With mice that did receive folic acid, this effect was only achieved with a dose that was 100 times higher: 30 mg/kg. In part considering the knowledge of the average skilled person about the competition between folates and antifolates, on the basis of those results the average skilled person would not assume without further research that the effect of pemetrexed is retained with the administration of folic acid.

4.67. Fresenius' argument that the results of preclinical research (and the results from phase I clinical research) also indicated that folic acid reduces certain side effects of pemetrexed and that, therefore, the administration of folic acid makes the administration of pemetrexed in higher doses possible must be disregarded. The fact remains that the results from preclinical research merely suggest that the effect of pemetrexed is retained with these high doses and that the results of the phase I clinical research cannot help the average skilled person further on that point according to Fresenius. In addition, Lilly argued without at least sufficient dispute that the mice experiment used, with cancer cells specifically designed to be sensitive to pemetrexed, has little predictive value for the relationship between toxicity and effectiveness. Therefore, the fact that the research results from the mice experiment suggest that high doses of pemetrexed combined with folic acid will reduce certain side effects of pemetrexed while the effect of pemetrexed on the specific cancer cells is retained does not lead to the conclusion that the average skilled person would assume, without additional research, that this will also be the case with regular cancer cells.

4.68. Fresenius' argument – that on the basis of the aforementioned results from preclinical research (and the results from the phase I clinical research), it was obvious for the person skilled in the art to investigate whether the administration of folic acid would reduce the side effects of pemetrexed without

detracting from the effectiveness of pemetrexed – can be disregarded. This is because the invention claimed by Lilly in EP 508 does not concern the combination of pemetrexed with just folic acid. The fact that the American and Japanese courts, among others, held that a patent claim that was aimed at that combination of pemetrexed with just folic acid lacked inventive step is therefore irrelevant, contrary to what Fresenius believes, to the assessment of the validity of EP 508.

4.69. Moreover, Fresenius has based the knowledge of the use of the combination of antifolates and folic acid on the American patent application from Grindey (US 5 217 974, Exhibit 78 submitted by Lilly), in which a mechanism was proposed for reducing the toxicity of a specific type of antifolate (including lometrexol) by means of pre-treatment using a certain type of protein binding agent, such as folic acid. Regardless of the fact that one patent application is insufficient to substantiate the alleged common general knowledge, it must be assumed that the teachings of this patent application were outdated on the priority date. Lilly drew attention to the later publication by Laohavinij (Annex 3 to Exhibit 58 submitted by Lilly), which describes much more extensive research into the combination of lometrexol and folic acid (Laohavinij's study was a clinical study with 43 patients, while Grindley contains the data of only one patient). In accordance with the scepticism asserted by Lilly regarding the effect of folic acid, Laohavinij expressly mentions the concern that the administration of folic acid will circumvent the effect of the antifolate or might even support tumour growth. The results of her research did not alleviate that concern. Laohavinij explains that the clinical response to lometrexol that was observed when only lometrexol was administered generally was not seen when lometrexol was administered in combination with folic acid. With the administration of folic acid, only one patient showed such a response.

4.70. Lastly, Fresenius appears to have attempted to substantiate the alleged knowledge about the combination of antifolates with folic acid with its assertion that the average skilled person knew that tumour cells are accelerating cells that need more folic acid than healthy cells. That assertion must be rejected. Lilly disputed that assertion with reasons and substantiation by means of expert statements. In that regard, Lilly pointed out aspects including that there are also healthy accelerating cells, like those in bone marrow and the intestinal tract, and that antifolates do not differentiate between healthy cells and cancer cells. Moreover, Fresenius merely substantiated the assertion with a quote from Chapter 12 of Jackman's bundle, in which the administration of folic acid is suggested as a measure that many normalise the response by repairing the folate pools in tissue with a low need for folate. That suggestion in Jackman is not substantiated with results from research. What is more, the suggestion is made in a chapter that discusses the antifolates lometrexol and LY309887. As established above, the average person skilled in the art knew on the priority date that clinical research into the combination of lometrexol with folic acid does not support the suggestion made in Jackman.

correlation folate and vitamin B12 and folate trap

4.71. Whether the knowledge of the correlation between folate and vitamin B12 alleged by Fresenius was part of the common general knowledge may remain moot. In so far as it was not, the inventive step challenge fails on that point alone, as Fresenius did not explain why the average skilled person would consult information about the correlation between folate and vitamin B12 and the folate trap. In so far as the knowledge referred to is part of the common general knowledge, this cannot lead to the opinion that the claimed invention lacks inventive step. On the basis of that knowledge, it is not obvious for the average skilled person to investigation with any expectation of success whether a deficiency in functional folate can be resolved by administering vitamin B12.

4.72. Contrary to what Fresenius suggests, it does not follow from the publications cited by Fresenius in substantiation of the alleged knowledge about the correlation between folate and vitamin B12 (Baynes, Exhibit 33 submitted by Fresenius, and Scott, Exhibit 34 submitted by Fresenius) that in treating cancer with pemetrexed, a problematic deficiency of function folate is seen, or that administration of vitamin B12

will always remedy a folate deficiency. Baynes' and Scott's publications describe that a deficiency in vitamin B12 results in folate (5-methyl-tetrahydrofolate or 5-MTHF) not being converted into functional folate (tetrahydrofolate or THF). From this, the average skilled person learns that the administration of vitamin B12 impacts the amount of functional folate *if* there is a vitamin B12 deficiency. Based on that knowledge, therefore, the average skilled person would merely expect effect from the administration of vitamin B12 in patients with a vitamin B12 deficiency.

4.73. The average skilled person will not find a pointer in Baynes and Scott that patients being administered pemetrexed have a deficiency in functional folate or in vitamin B12. This is because this information about the correlation between folate and vitamin B12 is not presented within the context of the treatment of cancer. They describe the correlation between folates and vitamin B12 in the context of haematological anomalies, such as megaloblastic anaemia and pernicious anaemia (types of anaemia) and neuropathy (nerve damage). This means that on the basis of these publications, the average skilled person only has reason to assume that there is a deficiency in functional folate when the hematologic anomalies described occur, and subsequently investigate whether that deficiency of functional folate was caused by a deficiency in vitamin B12. When treating cancer patients with pemetrexed, on the basis of these publications the average skilled person has no reason to assume that there is a deficit of functional folate that needs to be remedied. On the contrary: the average skilled person knew that therapeutic effect of antifolates like pemetrexed is based on the competitive relationship between antifolates and folates, and that the treatment with an antifolate in that sense is actually aimed at creating a deficit of functional folate (see 4.62 above). What is more, based on these publications the average skilled person has no reason to investigate whether the side effects of pemetrexed are caused by a possible deficit of vitamin B12. This is because it follows from the fact that this concerns side effects that they are caused by the administration of the antifolate pemetrexed, and Lilly argued, without dispute, that the average skilled person knew that pemetrexed impacts the DNA cycle rather than the cycle in which vitamin B12 plays a part.

4.74. If, despite the foregoing, the average skilled person were to study whether patients to whom pemetrexed is administered have a deficit of vitamin B12, they would have come across the publications by Niyikiza (Annex 11 to Exhibit 58 submitted by Lilly) and Zervos (Annex 12 to Exhibit 58 submitted by Lilly). These two publications teach the average skilled person that no correlation was observed between the specific biomarker for the status of vitamin B12 (methylmalonic acid or MMA) and the toxicity of pemetrexed. It was neither asserted nor shown that there are other publications that do disclose a correlation between the status of vitamin B12 and the toxicity of pemetrexed. In that light, it cannot be assumed to have been established that the average skilled person would expect patients to whom pemetrexed was administered had a deficit of vitamin B12 (also see para. 4.84 below regarding the alleged deficit of vitamin B12 in cancer patients in general).

4.75. In addition, the hematologic context in which the correlation between folate and vitamin B12 is presented entails that the knowledge about that correlation does not teach the average skilled person anything about the effect of administering vitamin B12 on the side effects and therapeutic effectiveness of pemetrexed. This is not changed by Fresenius' comment that in other parts of his book Baynes does discuss the treatment of cancer with antifolates and DNA synthesis. Those sections do not refer to the correlation between folates and vitamin B12, and the section that does describe the correlation between folates and vitamin B12 does not refer to the sections about the treatment of cancer using antifolates.

4.76. If the average skilled person were to assume nevertheless that the administration of vitamin B12 will lead to more functional folate, and were to link the increase in functional folate to the side effects and therapeutic effect of pemetrexed, this would still not lead them to the solution to the objective problem. Lilly put forward that the average skilled person would expect the alleged increase in functional folate to undermine the therapeutic effect of pemetrexed. In that context, Lilly referred to the knowledge of the average skilled person – as already explained above and as such not in dispute – about the competitive

relationship between folates and antifolates. Furthermore, the absence of any expectation of success by the average skilled person of maintaining the effectiveness of pemetrexed is supported by the expert statements submitted by Lilly (Chabner, Exhibit 71, O'Dwyer, Exhibit 64 and Calvert, Exhibit 58), all of whom stated that on the priority date they would have expected the opposite, and by the publications in the prior art that teach that the administration of vitamin B12 stimulates tumour growth (Vidal, Exhibit 5 and McLean, Exhibit 76 submitted by Lilly).

4.77. Fresenius did not assert that the average skilled person would believe that the administration of vitamin B12 would have the same effect on the side effects and therapeutic effect of pemetrexed as folic acid, or that the average skilled person would reasonably expect on the basis of the aforementioned results of the preclinical research involving the combination of folic acid and pemetrexed that the administration of vitamin B12 would reduce the side effects of pemetrexed while retaining the therapeutic effect. In so far as Fresenius meant to assert that the average skilled person would expect this on the basis of the correlation as described between folate and vitamin B12, absent any explanation or substantiation that assertion is rejected, also in light of what Lilly put forward regarding the differences between folic acid and vitamin B12.

4.78. Firstly, Lilly argued, as such without dispute, that folate administered through folic acid is a substrate within the context of the folate metabolism, meaning a substance that is consumed, while vitamin B12 is a cofactor in that process, meaning a substance that is not consumed but, rather, used repeatedly. In that light, it cannot be assumed that the average skilled person would automatically believe that the administration of vitamin B12 will have the same effect on the generation of functional folate as the administration of folic acid, let alone the same effect on the side effects and therapeutic effect of pemetrexed.

4.79. Secondly, Lilly explained that folic acid can circumvent the folate trap. According to Lilly, when folic acid is administered in high concentrations, the folate will penetrate the cell in inactive form and keep the DNA cycle going that is responsible for the side effects and therapeutic effect of pemetrexed. Starting from that premise, it cannot be assumed that the average skilled person would automatically believe that the administration of vitamin B12 will have the same effect on the generation of functional folate as the administration of folic acid, let alone the same effect on the side effects and therapeutic effect of pemetrexed.

4.80. Lilly substantiated the asserted circumvention of the folate trap by means of various expert statements and a reference to Scott's handbook, submitted by Fresenius itself (Exhibit 34 submitted by Fresenius), which explicitly describes that process. Fresenius and the expert engaged by it, Molloy, also do not appear to dispute that the folate trap is circumvented if folic acid is administered in high concentrations. Molloy's statement refers to the circumvention described by Scott as "*a situation that could occur where large doses folic acid are ingested*" and says it is "*biologically plausible*" that this circumvention works because folic acid penetrates the cell and participates in the DNA cycle (Molloy's statement, Exhibit 50 submitted by Fresenius, page 5). Fresenius did dispute that cancer patients would be administered high doses of folic acid. That refutation cannot succeed, already because in the clinical research into the combination of pemetrexed and folic acid, use was made of a dose of 3 mg or more, while according to Scott the circumvention is already seen with doses of 1 mg.

4.81. In addition, as established above, the results of the preclinical research into the combination of pemetrexed and folic acid does not automatically teach the average skilled person that the administration of folic acid reduces the side effects of pemetrexed while retaining its therapeutic effect. That uncertainty regarding whether the effectiveness of pemetrexed will be retained when folic acid is administered and the uncertainty described above regarding the effects of the administration of vitamin B12 as compared to the effects of the administration of folic acid, when viewed in conjunction, entail that it cannot be maintained

that it was obvious for the average skilled person to investigate, with a reasonable expectation of success, whether the administration of vitamin B12 will reduce the side effects of pemetrexed without diminishing its therapeutic effectiveness.

4.82. In itself, Fresenius rightly argued that in answering the question of whether the average skilled person would investigate the administration of vitamin B12, the scope of the possible reward must also be considered. Contrary to what Fresenius is arguing, however, in this case that factor does not unambiguously support Fresenius' position regarding the inventive step of the invention claimed in claim 2. Although the reward of a successful cancer treatment is considerable, Lilly argued with substantiation, and without dispute, that it was known on the priority date that clinical research had shown that the toxicity of pemetrexed – without vitamin B12 and folic acid – was bearable and manageable; research disclosing that pemetrexed did have very serious side effects was not published until after that date. Starting from the premise that the average skilled person assumed that the side effects of pemetrexed were reasonably under control, the average skilled person would have thought that there was relatively little to gain from a product that further reduced the side effects, and it must be assumed that their concerns in connection with maintaining the effect of pemetrexed carried relatively serious weight.

4.83. The fact that it was not obvious to the average skilled person to add vitamin B12 to a cancer treatment with a combination of antifolate and folic acid is confirmed by the fact that is established between the parties that vitamin B12 was not added in any of the clinical research that had been conducted on the priority date with the combination of an antifolate and folic acid. The documents Grindey (Exhibit 78 submitted by Lilly), Laohavinij (Annex 3 to Exhibit 58 submitted by Lilly), Rees (Annex 5 to Exhibit 58 submitted by Lilly), Hammond (Exhibits 39 and 40 submitted by Lilly) that describe that research do not suggest using vitamin B12, either. Vesta (Exhibit 52 submitted by Fresenius) and Carrasco (Exhibit 51 submitted by Fresenius) do describe administering a combination of folic acid and vitamin B12, but in the cases described in those publications, those vitamins were not administered in combination with the antifolate (see 4.63 above).

deficit vitamin B12

4.84. Fresenius' assertion that it was known that in general 15 to 20% of cancer patients have a deficit of vitamin B12 cannot lead to any other opinion.

As established above, the average skilled person knows that the deficit is not the cause of the side effects of pemetrexed, as supported by publications that do not disclose any correlation between the vitamin B12 status and the toxicity of pemetrexed, and the average skilled person would not reasonably expect that administering vitamin B12 would reduce the side effects of pemetrexed without reducing the therapeutic effect of pemetrexed. For that reason, the average skilled person would not opt for a combination of pemetrexed with vitamin B12 within the context of treating cancer.

4.85. Fresenius' assertion that over time, a deficit of vitamin B12 can lead to hematologic anomalies such as neutropenia cannot change this. That fact means that it was not obvious to the average skilled person when identifying a vitamin B12 deficit to make the administration of vitamin B12 part of the treatment of cancer using pemetrexed. On the contrary: because of the possible interaction with the antifolate, it is obvious to separate the treatment of said hematologic anomalies from the treatment with pemetrexed. This can be done on the one hand by assigning priority to the usually urgent need for a cancer treatment with pemetrexed over the treatment of health issues caused by a deficit of vitamin B12. With serious health issues as a result of a deficit of vitamin B12, it can be concluded on the other hand that the patient is not healthy enough for treatment with pemetrexed, in which case there will be no administration of a combination of folic acid and pemetrexed, either. The expert statements submitted by Lilly support the fact that both of these options, and not the combination therapy of pemetrexed with vitamin B12, were obvious to the average skilled person with the assumed observation of a vitamin B12 deficit.

no prejudice

4.86. Fresenius' argument that there was no prejudice against using vitamin B12 for the treatment of cancer can be disregarded. The assertion that there was no advantage to using vitamin B12 is insufficient to challenge the inventive step of the claimed invention.

4.87. The opinion above regarding the inventive step of the invention from claim 2 of EP 508 is not based on overcoming a prejudice. However, the scepticism put forward by Lilly regarding the retention of the effectiveness of pemetrexed when administering vitamin B12 and/or folic acid was taken into account in the assessment of Fresenius' assertion, for example, that the average skilled person knew of administering antifolates in combination with folic acid in order to reduce the toxicity of the antifolate without detracting from the effectiveness of the antifolate and Fresenius' assertion that it was obvious with a reasonable expectation of success to attempt to see whether a deficit of effective folate could be resolved by administering vitamin B12. Lilly also properly substantiated that scepticism by means of knowledge of the competitive relationship between folates and antifolates, which is not in dispute, and with expert statements and documents from the prior art.

problem-solution approach

4.88. In addition to the argumentation described above at 4.59, Fresenius put forward a challenge of the inventive step of the invention in claim 2 on the basis of the problem-solution approach. That reasoning cannot lead to the opinion that the invention lacks inventive step, either.

4.89. Whether Chapter 8 of Jackman's bundle *Antifolate Drugs in Cancer Therapy* (Exhibit 32 submitted by Fresenius; hereinafter: Jackman), in light of the aforementioned scepticism of the average skilled person regarding the effect of administering folic acid, can be deemed the closest prior art, meaning a realistic point of departure for the assessment of the inventive step, may remain moot. If it were to be assumed with Fresenius that this is the case, then this cannot lead to the conclusion that the invention claimed in claim 2 lacks inventive step, for the following reasons.

4.90. Chapter 8 of Jackman describes, for example, the preclinical research discussed above into the combination of pemetrexed and folic acid in mice. The most important difference with the invention claimed in claim 2 of EP 508 is the use of vitamin B12 or a pharmaceutically acceptable derivative thereof. It is not in dispute that the effect of that additional measure is a reduction of the toxic side effects of pemetrexed while retaining its therapeutic effective. Departing from this, the objective problem that is solved by the invention claimed in claim 2 must be reducing the toxic side effects of pemetrexed while retaining its therapeutic effect. Fresenius starts from this assumption as well.

4.91. Fresenius argued that in order to solve the objective problem, the average skilled person would look at the improvement suggested for comparable antifolates. In that regard, Fresenius refers to Chapter 12 of the same bundle by Jackman (Exhibit 32 submitted by Fresenius). There, the description of the antifolates lometrexol and LY309887 discuss, for example, "*modulating antifolate toxicides through vitamin supplementation*", also reporting that "*the biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B12 and B6*". Based on this information, the invention claimed in claim 2 is not obvious, for the same reasons as those on the basis of which this was ruled above based on the knowledge of the correlation between folic acid and vitamin B12 (see para. 4.72 et seq. above). On the basis of this information as well, the average skilled person would have no reasonable expectation that the administration of vitamin B12 will reduce the side effects of pemetrexed without diminishing the effect of pemetrexed, also in light of the scepticism that existed regarding the effect of administering vitamin B12.

4.92. What is more, Lilly rightly argued that the average skilled person will understand that the cited sections from Jackman are suggestions that are not substantiated with research. In the chapter referred to,

Jackman even explicitly reports that the folate status of cancer patients has not been systematically evaluated. Also in view of the scepticism that existed regarding the effect of administering vitamin B12, on the mere basis of such an unsubstantiated suggestion, the average skilled person would not reasonably expect to solve the objective problem by adding vitamin B12 to the combination of pemetrexed and folic acid.

4.93. Moreover, before considering the addition of vitamin B12 to a treatment with pemetrexed, the average skilled person would investigate whether more is known about the other antifolates described in Jackman. They would then come across the publication by Laohavinij already discussed above, which describes clinical research investigating the combination of lometrexol and folic acid (Annex 3 to Exhibit 58 submitted by Lilly). As held above, in her publication Laohavinij explicitly expressed the concern that administration of folic acid will circumvent the effect of the antifolate or might even support tumour growth, and the results of her research do not alleviate that concern. Moreover, it is not in dispute that the average skilled person knew on the priority date that the development of lometrexol had been suspended. The asserted pointer from Jackman therefore leads the average skilled person to a dead end.

conclusion on inventive step

4.94. Based on the foregoing, the conclusion must be that Fresenius' attack on the inventive step of claim 2 of EP 508 is unsuccessful. This entails that the claim must be deemed valid. Matters thus standing, the validity of the other claims of EP 508 need no discussion, as infringement of claim 2 of EP 508 is sufficient for awarding Lilly's claims, and Fresenius' claim seeking nullity of the patent is not at issue.

4.95. This outcome concurs with the decision cited by Lilly of the Opposition Division of the European Patent Office regarding EP 508 (Exhibit 7 submitted by Lilly) and with the opinion of the Swiss court regarding the Swiss part of EP 508 (Exhibit 48 submitted by Lilly) – and with the opinions of the American and Japanese courts regarding the parallel American and Japanese patents. The Court of Appeal is aware that the outcome is not in line with the opinion of the German Bundespatentgericht regarding the German part of EP 508. However, based on the assertions and evidence submitted by the parties in these proceedings, the Court of Appeal cannot endorse the conclusion of the German court that the invention claimed in claim 2 was obvious to the average skilled person.

claims

4.96. Assuming that Fresenius' product falls under the scope of protection of claim 2 of EP 508, and that the claim is valid, the conclusion must be that by trading that product Fresenius has infringed the patent. This is because Fresenius has explicitly acknowledge that it knows that its product is used in combination with vitamin B12 and folic acid for the treatment of cancer (Statement of Defence, para. 21 at b). In that light, Fresenius has directly infringed the patent, because Fresenius foresaw that the medicinal product it manufactured intentionally would be used for the treatment foreseen by the patent (slowing tumour growth), and/or indirectly infringed the patent, because Fresenius offered the product and supplied it to persons who were not entitled to apply the invention while knowing that its product was suitable and intended for the patented indication.

4.97. Given the foregoing ruling on the infringement, Lilly's injunction against infringement may be awarded. It does not follow from Lilly's assertion that Fresenius acted illegally otherwise. The injunction against unlawful action will not be awarded for that reason.

4.98. Lilly has not explained its interest in the declaratory decision sought alongside the injunction to be awarded and the order to compensate damage, not even after Fresenius argued that Lilly has no interest in this. Therefore, that claim will be denied due to a lack of interest.

4.99. Fresenius rightly adduced that an accountant cannot certify Fresenius' statement on the basis of the rules of the accounting profession. The principal claim must be denied for that reason. In the alternative, Lilly sought a report of findings by an accountant. Fresenius did not argue that this is also unfeasible or that Lilly has no interest in this. The claim will be awarded in its alternative form for that reason.

4.100. Regarding the substance of that report, Fresenius rightly argued that Lilly has no interest in a renewed version of the data that Fresenius has already provided to Lilly in performance of the judgment in the preliminary relief proceedings (the data sought at a, b and c). After that date, the injunction imposed with that judgment initially applied. Although that temporarily was not the case with the District Court's judgment against the claimant in this case, Fresenius argued that since the judgment in the preliminary relief proceedings it no longer performed any reserved act in the Netherlands, which was not disputed. This is why it must be assumed that Lilly has no interest in this report, and exclusively the report on the profits enjoyed will be awarded (the data sought at d).

4.101. In view of the fact established above that Fresenius performed no reserved acts in the Netherlands after the judgment in the preliminary relief proceedings and considering the time that has passed since that judgment, there is no cause for the product recall sought. Nor can it be assumed that Lilly has an interest in the rectification sought, in view of what Fresenius put forward in that regard, which was not disputed.

4.102. Penalties subject to non-compliance will be issued with the injunctions and orders to be awarded. To avoid execution disputes, the penalties subject to non-compliance for the injunction will be capped at EUR10,000,000.00 and for the other orders at EUR 1,000,000.00.

4.103. The damages and disgorgement of profits sought will also be awarded, it being understood that the disgorgement of profits will not cumulate with the compensation of damage comprising lost profit. In the separate proceedings for the determination of damages, therefore, Lilly will have to choose between disgorgement of profit and compensation of damage comprising lost profit, in addition to the compensation of any other damage. Fresenius' argument that it did not know and reasonably could not have known that it was infringing must be rejected. Fresenius did not contest that Lilly had informed it on several occasions that it was infringing. The error made by Fresenius on the basis of foreign judgments – set aside later – in respect of the scope of protection of EP 508 must be at its own expense.

4.104. Being the largely unsuccessful party, Fresenius will be ordered to pay the costs of the proceedings in the first instance, the principal appeal and the cross-appeal. The parties have agreed that the reasonable and proportionate costs of the proceedings at first instance and of the preliminary relief proceedings conducted between the parties in two instances can be estimated at EUR 400,000. Because Lilly already sought payment of EUR 150,000 in the preliminary relief proceedings, it is entitled to EUR 250,000 for the first instance in these proceedings on the merits. As regards the appeal in these proceedings on the merits, the parties have agreed that the costs should be estimated at EUR 300,000 for the principal appeal and the cross-appeal jointly. The Court of Appeal see no reason to deviate from that estimate.

4.105. Lastly, as it has been established without dispute that in performing the costs order from contested judgment, Lilly has paid EUR 400,000 to Fresenius. The claim seeking repayment of that amount can be rewarded, as well.

5. The decision

The Court of Appeal

5.1. sets aside the judgment rendered between the parties by the District Court in The Hague of 19 July 2019 and, adjudicating again:

5.1.1. orders Fresenius, with immediate effect after services of this judgment, to cease and desist from any direct or indirect infringement of EP 508 in the Netherlands, on penalty of forfeiting a file subject to non-compliance of EUR 100,000 for each day or part of a day that Fresenius fails to comply with the order in part or in full or, at Lilly's discretion, in the amount of EUR 100,000 for each infringing product with which Fresenius fails to comply with the order, in part or in full, up to a maximum of EUR 10,000,000;

5.1.2. orders Fresenius to provide within 21 days after services of this judgment, addressed to Lilly's counsel, a complete, correct and verifiable report of the profits enjoyed by Fresenius as a result of the infringing acts in the Netherlands, specified for each infringing product that was sold and/or delivered, all supported by means of legible orders, order confirmations, invoices and copies of other records and documentation of purchases and sales in substantiation of any deductions in the sales and profits to be reported;

5.1.3. orders Fresenius to provide within 21 days after services of this judgment, addressed to Lilly's counsel, a complete, correct and verifiable report of factual findings, drawn up by an independent registered accountant, with whom and with whose firm Fresenius has no previous relationship, with the findings regarding the amount, estimated or otherwise, of the profits realised by Fresenius as a result of the infringing activities in the Netherlands, which report must contain factual findings regarding the data and records mentioned above in 5.1.2;

5.1.4. orders Fresenius to pay an immediately payable fine subject to non-compliance of EUR 25,000 for each violation by Fresenius of the orders imposed at 5.1.2 and 5.1.3, or – at Lilly's complete discretion – for each day that Fresenius acts in violation of these orders, up to a maximum of EUR 1,000,000;

5.1.5. orders Fresenius to compensate Lilly for the damage suffered and to be suffered by Lilly as a result of the infringement by Fresenius of EP 508 in the Netherlands or – at Lilly's discretion – the profits realised and to be realised by Fresenius as a result of the infringement of EP 508 in the Netherlands, all to be established in follow-up proceedings and settled according to the law, increased by the statutory interest as from the day of the summons until the day of payment in full;

5.1.6. orders Fresenius to pay the costs of the proceedings at first instance, estimated at EUR 250,000, also determining that if those costs are not paid within two weeks after service of this judgment, Fresenius will owe statutory interest without further demand;

5.1.7. denies Lilly's additional or other claims;

5.2. orders Fresenius, in order to repay that which Lilly paid to Fresenius in compliance with the aforementioned judgment, to pay an amount of EUR 400,000 to Lilly, increased by the statutory interest on that amount as from 11 July 2019;

5.3. orders Fresenius to pay the costs of the principal appeal and the cross-appeal, estimated to this day at EUR 300,000, also determining that Fresenius must pay statutory interest on these costs of the proceedings as from two weeks after the date of this judgment;

5.4. declares this judgment immediately enforceable regardless of any appeal.

This judgment was rendered by Justices P.H. Block, J.W. Frieling and M.W.D. van der Burg, and was signed and pronounced in open court by Justice J.E.H.M. Pinckaers, cause-list justice, on 27 October 2020, in the presence of the court clerk.