Unofficial machine translation

Judgment

COURT OF APPEAL THE HAGUE

Civil law division
Case number: 200 261 833/01
Case number of the District Court : C/09/541424/ HA ZA 17-1097

judgment of 27 October 2020

in the matter of

Eli Lilly and Company,
established in Indianapolis, Indiana, United States of America,
claimant in principal appeal,
defendant in cross appeal,
Hereinafter referred to as: Lilly,
Attorney: K.A.J. Bisschop in Amsterdam,

versus

Fresenius Kabi Nederland B.V.,
established in 's-Hertogenbosch,
defendant in principal appeal,
claimant in cross appeal,
Hereinafter referred to as: Fresenius,
Attorney: P.L. Reeskamp, Amsterdam.

1 The proceedings

1.1. The Court of Appeal has taken note of the following procedural documents:
- the file on the proceedings at first instance;
- the writ of summons on appeal of 19 June 2019;
- the statement of appeal also containing an increase of claim (including exhibits);
- the statement of defence also the statement of appeal in the cross appeal (with exhibits);
- the statement of defence in cross appeal (with exhibits);
- the Act containing additional exhibits and amending claim from Lilly with exhibits 79 to 89;
- the Act containing additional exhibits by Fresenius with exhibits 44 to 52;
- the Act containing additional exhibit of Lilly with exhibit 90;
- notice from Lilly's lawyer that the parties have reached an agreement on the amount of the costs of proceedings on appeal; and
- the oral hearing of 20 January 2020.

1.2. Further to a request by Fresenius, the Court of Appeal decided to extend the oral hearing time available to the parties to the oral proceedings from the 45 minutes in the initial period usual for patent cases for each side to 60 minutes in the initial period for each side. Fresenius' requests for a further extension of the oral hearing time were rejected by the Court of Appeal.

1.3. Judgment was scheduled for today.

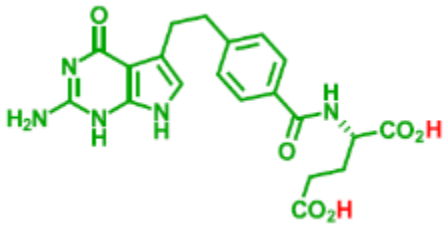
2 The facts

2.1. The facts established by the District Court in its judgment of 19 June 2019 are not in dispute. The Court of Appeal will also base itself on those facts, with the overview of jurisprudence supplemented by recent rulings. This case concerns the following.

Pemetrexed, Lilly and Alimta®

2.2. Pemetrexed is an antifolate. Antifolates are so-called antineoplastics. This means that they prevent the formation of (cancer) tumours. Antifolates not only have (an inhibiting) effect 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 side effects (toxicity).

2.3. The substance pemetrexed is (due to the presence of two -CO2H groups) 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.

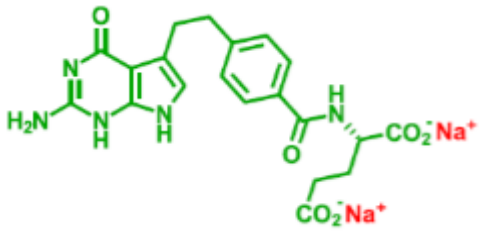
2.4. When pemetrexed diacid is introduced into an aqueous solution, the hydrogen atoms indicated in red are separated as positively charged ions from the rest of the molecule, which is then a negatively charged ion (also known as anion). Only the anion is responsible for the activity (and toxicity) of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

2.5. Lilly is part of the Lilly group that is active in the research, development and marketing of new medicines.

2.6. Lilly is marketing the pemetrexed disodium medicine Alimta®, indicated for the treatment of certain lung cancers (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. The "Summary of Product Characteristics" (hereinafter in the English abbreviation: 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 -CO2Na 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 introduced into 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. Again, only the anion is responsible for the activity (and toxicity) of the antifolate.

2.10. It is not possible to produce a form of administration of pemetrexed consisting only of the anion; only a neutral substance can be handled and this implies the presence of a cation (a positively charged particle, which forms a salt) or hydrogen (which forms the diacid).

2.11. The antifolate pemetrexed, i.e. both the diuretic and pharmaceutically acceptable salts of pemetrexed such as the disodium salt, was initially protected by EP 0 432 677 (hereinafter EP 677), of which Lilly was (co-)holder. EP 677 is the basic patent for Supplementary Protection Certificate 300181 for 'pemetrexed, if desired 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 proprietor of European patent 1 313 508 B1 ('EP 508'), entitled '*Combination containing an antifolate and methylmalonic acid lowering agent*'. EP 508 was granted on 18 April 2007 in an international application filed on 15 June 2001 under number PCT/US2001/014860 (hereinafter: the PCT application or the original application) published as WO 02/02093 A2 (hereinafter: WO 093). This made use of priority 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 dependent claims (2 to 11 and 13 to 14). In the original English language they read as follows:

> 1. Use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin.
>
> 2. Use according to claim 1 wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin, and a folic binding protein binding agent selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5-forinyl-5,6,7,8-tetrahydrofohc acid or a physiologically available salt or ester thereof.
>
> 3. Use according to claim 2 wherein the folic binding protein binding agent is folic acid.
>
> 4. Use according to any one of claims 1 to 3 wherein the vitamin B12 or pharmaceutical derivative thereof is vitamin B12, cobalamin or chlorocobalamin.
> 5. Use according to any one of claims 1 to 3 wherein the vitamin B12 or pharmaceutical derivative thereof is selected from vitamin B12 or hydroxocobalamin.
>
> 6. Use according to any one of claims 1 to 5 wherein the medicament, the vitamin B12 or pharmaceutical derivative thereof and optionally the folic binding protein binding agent are to be administered simultaneously, separately or sequentially.
>
> 7. Use according to any one of claims 1 to 6 wherein the medicament is to be administered after administration of the vitamin B12 or pharmaceutical derivative thereof.
>
> 8. Use according to any one of claims 1 to 7 wherein the medicament is to be administered after the folic binding protein binding agent.
>
> 9. Use according to any one of claims 2 to 8 wherein the medicament is to be administered after pretreatment with the vitamin B12 or pharmaceutical derivative thereof followed by folic acid.
>
> 10. Use according to any one of claims 1 to 9 wherein vitamin B12 or pharmaceutical derivative thereof is to be administered as an intramuscular injection.

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

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

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

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

2.14. In the undisputed Dutch translation, the claims of EP 508 are 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. In the description of the patent - insofar as relevant here - the following has been included:

[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 mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (...)

[0004] Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (...). The role of folic acid in modulating the toxicity and efficacy of the multitargeted antifolate LY 231514 (pemetrexed) was discussed in Worzalla *et al*. (Anticancer Research 18: 3235-3240 (1998) Worzalla JF, Chuan S and Schultz RM). EP-A-0546870 relates to nutrient compositions which are intended to prevent and cure infectious diseases and which are intended to be administered to patients being administered with anticancer drugs to prevent and treat infectious diseases due to immunosuppression induced by the anticancer drug therapy. The compositions of EP-A-0546870 are characterized in that they comprise a certain amount of retinoid compound(s) such as vitamin A which is indicated as being responsible for the immunoreactivity. Effects of vitamin B12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations (Lancet 1995; 346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

[0005] Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent as vitamin B12, without adverse [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 attorney, Dr I.J. Burnside ('Burnside'), asked the European Patent Office (EPO) to consider the PCT application on the basis of the documentation on the basis of which the *International Preliminary Examination* was carried out. In doing so, he replaced the original claims contained in the PCT application with a new set of claims (1 to 17), the new claim being claim 1:

> 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. In Communication of 9 March 2004, the EPO examiner indicated, among other things, that the subject matter of the new claims 1 to 9, 11 to 14 and 16 lacks novelty in the light of documents D1 (EP 0 546 870) and D2 (US 5 405 839) because - in short - the use of an antifolate, namely 5-fluorouracil and methotrexate, in combination with vitamin B12 (a *methylmalonic acid lowering agent*) had already been revealed therein.

2.18. By fax of 23 December 2004, Burnside again submitted a new set of claims, informing the EPO as follows:

> 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 amended set of claims submitted by Burnside were, in so far as relevant, as follows:

> 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 of 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 as follows, where 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 ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFIT") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, IN) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

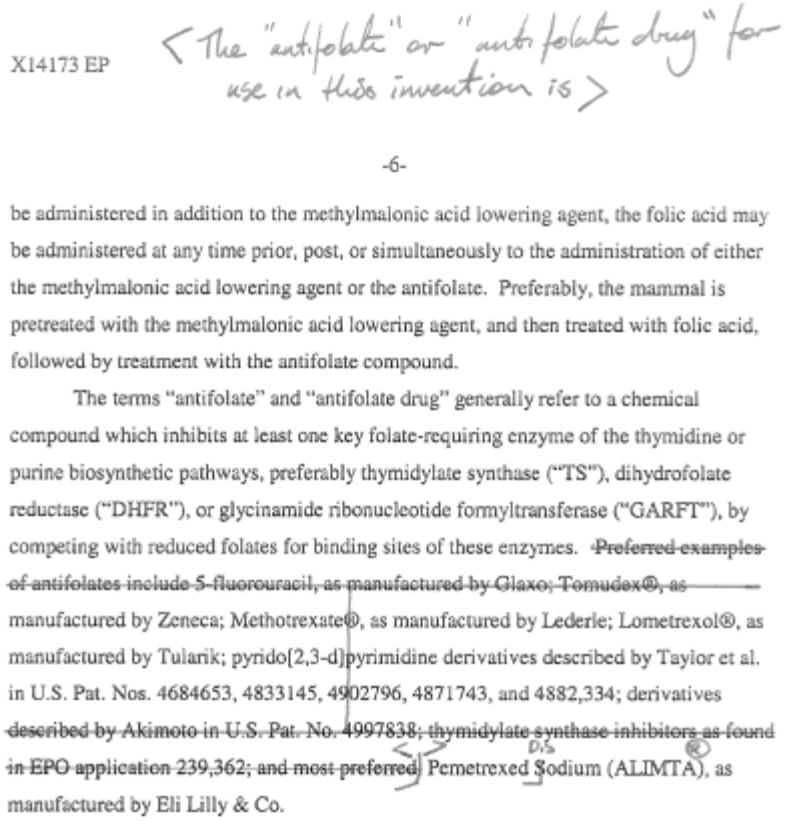
Lines 6-16 on page 6 read as follows:

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 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; 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 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.

2.22. By letter dated 8 March 2006, Burnside submitted the claims currently in force and informed the *examiner, inter alia, 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 aforementioned letter contains a copy of the description from the PCT application, handwritten by Burnside, including the following changes (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 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; 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 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.

2.24. The EPO *communication* 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* handwritten the adjustments himself/herself in the so-called '*Druckexemplar*'.

2.25. By letter dated 2 February 2007, Burnside informed Lilly, on behalf of Lilly, that it accepted these changes in the description:

> 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 proprietor of European patent EP 1 265 612 B1 ('EP 612'), which was granted on 26 May 2004, following an application made on 23 January 2001, for a *'Pharmaceutical composition comprising pemetrexed together with monothioglycerol', L-cystein or thioglycolic acid'*. Paragraph [0020] of the description of this patent mentions:

> 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 pyridinum salts. The substituted ammonium salts are one especially preferred group of salts.

Burnside was also involved in the granting of that patent as Lilly's patent attorney.

Fresenius and Pemetrexed Fresenius

2.27. Fresenius is part of the Fresenius group. It is active in the pharmaceutical market and markets several generic medicines for intravenous administration worldwide.

2.28. One of the products of the Fresenius group is 'Pemetrexed Fresenius Kabi' ('Pemetrexed Fresenius') which is indicated for malignant mesothelioma of the pleura and not small cell lung carcinoma.

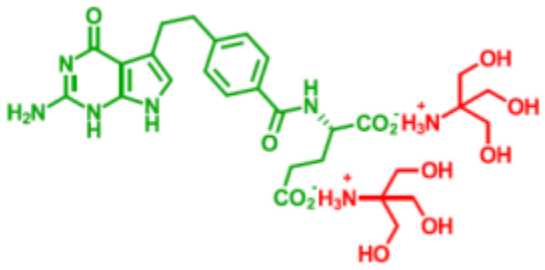
2.29. The SmPC of this generic product states that Fresenius is the representative of the marketing authorization holder Fresenius Kabi Oncology Plc. in the Netherlands. The latter obtained the marketing authorisation by applying the centralised procedure as referred to in Article 3.3 of Regulation EC 726/2004.1 Reference is made to Lilly's product Alimta® as a reference product.

2.30. Pemetrexed Fresenius, like Alimta® , has the pharmaceutical form of a (freeze-dried) powder for concentrate for solution for intravenous infusion. The same excipients have been used for the formulation as for Alimta®, it being understood that the excipient tromethamine is used instead of sodium hydroxide. In the SmPC of Pemetrexed Fresenius the following is included under section 4.2 (posology and route of administration):

To reduce toxicity, patients treated with pemetrexed should also be given vitamin supplements (see section 4.4). Patients should take oral folic acid or a multivitamin preparation containing folic acid (350 to 1000 micrograms) daily. At least five doses of folic acid must be taken during the seven days prior to the first dose of pemetrexed and continued throughout the 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 preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections can be administered on the same day as pemetrexed.

The SmPC also states that the powdered product 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, with red marked tromethamine groups that are separated from the rest of the molecule as cations when brought into 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. Between Lilly, on the one hand, and Fresenius or other suppliers of generic pemetrexed products, on the other hand, several proceedings have been conducted in Europe concerning (non-)infringement of EP 508, including the proceedings described below.

The Netherlands

2.35. In the Netherlands, the preliminary relief judge of the District Court of The Hague, by judgment of 1 March 2017, imposed an injunction on Sandoz B.V., 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 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 upheld by this Court of Appeal by judgments of 8 May 2018 (ECLI:NL:GHDHA:2018:1106 and ECLI:NL:GHDHA:2018:1105). Fresenius filed supreme appeal against the judgment delivered against her. The Court of Appeal is of its own motion aware that the Supreme Court dismissed the supreme appeal by judgment of 12 June 2020 (ECLI:NL:HR:2020:1036).

2.36. Sandoz B.V. has instituted invalidity proceedings in respect of EP 508 before the District Court of The Hague. The proceedings were adjudicated on 16 January 2019 (ECLI:NL:RBDHA:2019:321), in which the claims were dismissed. Sandoz B.V. lodged an appeal against that judgment. That appeal had not yet been decided at the time of the oral hearing in this case.

United Kingdom

2.37. Actavis UK Limited and Others (now Teva) brought infringement proceedings against Lilly before the High Court in 2012. It sought a declaratory judgment that the marketing of certain 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 his judgment of 15 May 2014, Justice Arnold ('Arnold J') granted a declaration of non-infringement, considering that the products listed by Actavis do not directly or indirectly infringe EP 508.

2.38. On appeal, the Court of Appeal upheld Arnold J's ruling of 25 June 2015 (by Lord Justice Floyd with the consent of Kitchin LJ and Longmore LJ) that there was no direct infringement. However, Arnold J's ruling was partially overturned as regards the indirect infringement finding. According to the Court of Appeal, if the pemetrexed products mentioned by Actavis are diluted in a saline solution (with sodium chloride), this is an indirect infringement of EP 508. The question whether there is also indirect infringement when it is recommended that the pemetrexed diacid or the dipotassium salt be diluted in a dextrose solution has been referred back to the High Court.

2.39. The UK Supreme Court ('UKSC'), by judgment of 12 July 2017 (leading speech by Lord Justice Neuberger), held that the scope of protection of EP 508 extends to salts other than pemetrexed disodium, so that the pemetrexed products referred to by Actavis directly infringe EP 508.

Germany

2.40. Lilly brought interim relief proceedings against Fresenius before the Landgericht München. By judgment of 29 November 2016, the Landgericht found that there had been an infringement.

2.41. Lilly also initiated infringement proceedings against Actavis (now: Teva). In a judgment of 3 April 2014, the Landgericht Düsseldorf ruled that pemetrexed dipotassium (from Actavis) as an equivalent directly infringes the German part of EP 508. On appeal, the Oberlandesgericht Düsseldorf, by judgment of 5 March 2015, held that the scope of protection of EP 508 is limited to pemetrexed disodium, so that the use of pemetrexed dipotassium does not constitute a direct infringement, even on the basis of equivalence. On appeal in cassation, the Bundesgerichtshof ('BGH'), by judgment of 14 June 2016, referred the case back to the Oberlandesgericht Düsseldorf on the ground that the Oberlandesgericht had not correctly applied the German doctrine of equivalence. Due to a settlement between the parties, there will be no ruling in the case referred back.

2.42. Lilly sought an *ex parte injunction* against Ratiopharm (also part of the Teva group), which was granted by the Landgericht München on 6 April 2016. On 24 June 2016, following an *inter partes* hearing, the Landgericht München upheld the interim prohibition finding that Ratiopharm's pemetrexed diacid directly infringed EP 508 as an equivalent. By judgment of 18 May 2017 on appeal, the Oberlandesgericht München upheld the decision of the Landgericht München.

2.43. By judgment of 18 July 2018, the Bundespatentgericht declared the German part of EP 508 invalid further to a claim of Hexal, Strada and Ratiopharm. Lilly appealed against the judgment. At the time of the oral hearing in this case, that appeal had not yet been decided.

2.44. By judgment of 3 April 2019, the Landgericht München lifted the injunction against Fresenius and an injunction against Zentiva Pharma. On appeal, the Oberlandesgericht München upheld that decision.

Switzerland

2.45. By judgment of 9 March 2017, the Bundespatentgericht granted a declaration of non-infringement claimed by Actavis for pemetrexed products (dipotassium, ditromethamine or diacid). On 20 October 2017, the Bundesgericht, the highest Swiss court, set aside on appeal the decision of the Bundespatentgericht and held that the product marketed by Actavis, Amtiris® (which is the same product as Armisarte®) infringes EP 508. The Bundesgericht referred the case back to the Bundespatentgericht to assess whether the two products not marketed by Actavis, pemetrexed dipotassium and pemetrexed ditromethamine as freeze-dried product (which is the same product as

Fresenius'), also infringe EP 508. On 21 December 2017, the Bundespatentgericht found that these products also infringed EP 508.

2.46. Sandoz brought invalidity proceedings against the Swiss part of EP 508. The Bundespatentgericht ruled on 15 October 2019 that EP 508 was valid and dismissed the claim.

Denmark

2.47. On 8 December 2017, the Danish Maritime and Commercial Court granted a preliminary injunction against Fresenius Kabi claimed by Lilly. By judgment of 20 December 2018, the Ostre Landsret upheld this ruling.

Austria

2.48. On 22 December 2017, following the earlier rejection of an *ex parte* injunction sought by Lilly, the Handelsgericht Wien imposed an injunction on Fresenius in *inter partes* interim relief proceedings. By judgment of the Oberlandesgericht Wien of 12 April 2018, the infringement injunction was upheld. Proceedings on the merits between the parties are pending before the Handelsgericht Wien.

Finland

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

Sweden

2.50. On 31 January 2018, the Tingsrät Stockholm granted an injunction requested by Lilly against Actavis.

2.51. Lilly also brought an application for interim measures in Sweden against Fresenius. By judgment of 23 March 2018, the Tingsrät Stockholm assumed infringement. Proceedings on the merits between the parties are still pending before the same court.

Italy

2.52. In summary proceedings brought by Fresenius against Lilly before the District Court of Milan to obtain a declaration of non-infringement, the District Court ruled on 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 generic Pemetrexed Fresenius infringes the Italian part of EP 508. Other proceedings on the merits between the parties are still pending before the same tribunal.

Belgium
2.53. By judgment of 29 January 2019, the Brussels Court of Appeal annulled a judgment of the Commercial Court of 15 June 2018 rejecting an injunction 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 Lisbon Arbitration Tribunal found infringement in a case brought by Lilly against Fresenius. Fresenius has not lodged an appeal against that judgment.

3 The dispute

3.1. At first instance, Lilly claimed - in summary - that the District Court, as far as possible notwithstanding appeal, both by way of provisional relief and as an order in the main proceedings, grant an injunction against Fresenius prohibiting infringement in the Netherlands and order Fresinius to cease and desist any unlawful act against Lilly, on pain of a penalty payment, and furthermore, in the main proceedings, to declare that Fresenius infringed EP 508 in the Netherlands, with ancillary claims, including making a statement, sending a letter of rectification to its customers and publishing a

rectification on its website, and to order Fresenius to pay compensation for the damage suffered by Lilly and to surrender profits, and to order Fresenius to pay the full costs of the proceedings, plus statutory interest.

3.2. By judgment of 19 June 2019, the District Court dismissed Lilly's claims on the ground that Pemetrexed Fresenius does not fall within the scope of protection of the patent. In the District Court's opinion, the reasonable degree of legal certainty would not be sufficiently achieved if, despite the specific wording 'pemetrexed disodium' in the claims and the description 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 having increased the claim, that the Court of Appeal should set aside the judgment of the District Court and allow the claims of Lilly and order Fresenius to repay what Lilly has paid in compliance with the judgment, increased by statutory interest, with an order that Fresenius pay the full costs of the proceedings in both instances in accordance with Section 1019h of the Dutch Code of Civil Procedure (hereinafter referred to as "the Code of Civil Procedure") and stipulating that Fresenius must pay statutory interest on the costs of the proceedings from two weeks after the date of the judgment. In addition, on appeal, Lilly increased its claim by a subsidiary variant of the account statement claimed. Lilly puts forward eleven grounds of appeal, with which it seeks to bring the dispute before the Court in its entirety. Fresenius disputes Lilly's grievances and puts forward six cross-appeal grounds.

4 The assessment of the appeal

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

Article 69(1) of the European Patent Convention (hereinafter referred to as the EPC), which applies here pursuant to Article 2(2) of the EPC, provides as follows:

> The extent of protection of the European patent shall be determined by the claims. Nevertheless, the description and drawings shall be used to interpret the claims.

The Protocol on the interpretation of Article 69 of the Convention, annexed to Article 69 of the EPC (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 person skilled in the art, 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 extent 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)(b) of the Vienna Convention that, in addition to the context, account must be taken of any subsequent use in the application of the Convention which has given rise to agreement between the contracting parties on the interpretation of the Convention, with the result that prevailing views in the case-law and literature of the contracting parties also constitute a primary means of interpretation of the Convention.

4.3. In case law and literature, the following two approaches can be distinguished in the way 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 described in the conclusions 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. In the first step, an interpretation of the patent claim determines 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 reflected in the product or process, a second step determines 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 characteristics 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 where equivalence is tested separately.

4.4. Examples of both approaches described above can be found in Dutch case law. In other EEA member states the two-step approach described in 4.3.1 is currently the prevailing view. A two-step approach is established case law in, among others, Germany and France. In the UK the one-step approach as described under 4.3.2 was until recently followed, but in its judgement of 12 July 2017 in the Actavis - Lilly case the UKSC explicitly opted for the two-step approach (see paragraph 2.39). In view of this, it must be assumed that the two-step approach is currently also the prevailing view in the UK. Now that the two-step approach prevails in other EPC member states and also has a basis in Dutch case law, the Court 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 refer to the extreme referred to in Article 1 of the Protocol, where the scope of protection of the European patent is strictly determined by the literal text of the claim, but to an interpretation of the patent claims in the light, inter alia, of the description and drawings from the point of view of the average person skilled in the art with his knowledge of the state of the art (Article 69(1) EPC and the middle of Article 1 of the Protocol). This step alone does not take into account the possible equivalence of elements of the product or process to characteristics of the patent claims in accordance with Article 2 of the Protocol.

4.6. The second step concerns the question whether in the perception of the average person skilled in the art the claims, read in the light of the description and the drawings, leave room for equivalents, taking into account, on the one hand, an equitable protection of the patent holder and, on the other hand, a reasonable degree of legal certainty for third parties. 2

4.7. In order to be able to answer the aforementioned equivalence question positively, it is first of all required that the deviating element is technically equivalent to the claimed characteristic. This 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 as the claimed characteristic in that context. This requirement of 'technical equivalence' forms the basis for invoking 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 which the patent proprietor has made to the state of the art. In addition to the novelty and inventive step of the variant, which will be discussed separately below as a fourth requirement, that means that the invention must have been disclosed in the patent document in such a way as to make it obvious to the average person skilled in the art to use that invention also with elements which differ from the characteristic of the patent claim. In other words, the patent document must disclose to the average person skilled in the art a teaching that may include the application of equivalents.

4.9. This requirement does not mean that every equivalent must be sufficiently disclosed to the average person skilled in the art on the priority or application date. In the context of the question as to whether there is an equivalent element, importance can in fact also be attached to the knowledge of the average

person skilled in the art at the time of the infringement.3 In addition, when assessing the relationship between the scope of protection and the contribution to the state of the art, account must be taken of the degree of renewal brought about by the patent, because a high degree of renewal can impede the applicant's ability to adequately foresee and describe all embodiments. 4

4.10. Thirdly, it needs to be assessed whether recognition 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. In view of the fact 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 description and drawings, and the ambiguity created by the wording of the claims is, in principle, to the detriment of the patent proprietor. However, the use of terms in the patent claims which do not include equivalents verbatim cannot suffice for it to be considered that legal certainty for third parties is insufficiently ensured. If that were the case, reliance on equivalence would be impossible. Such an outcome would not be in line with Article 2 of the Protocol, which requires due account to be taken of equivalents. Recourse to equivalence should therefore be possible if, despite the specific wording of the conclusions, a sufficient degree of legal certainty is ensured. There is a sufficient degree of legal certainty if the average person skilled in the art understands that the patent claims leave room for equivalents because, for the average person skilled in the art, the teaching of the patent is clearly broader than the wording of those claims and there is no good reason in the eyes of the average person skilled in the art to limit the scope of protection to the application of the feature contained in the claims. Such a good ground does not exist only if the average person skilled in the art is entitled to assume that part of the protection has been waived.

4.11. Fourthly, if the defence gives cause to do so, it must be assessed whether the variant is new and inventive in relation to the state of the art of the patent. Granting protection for non-new or non-inventive products or processes would go beyond what justifies equitable protection for the patentee (also known from the Gillette or Formstein defence, named after two cases of the same name from England and Germany respectively). These aspects must be examined in the context of determining the scope of protection of the patent, since the novelty and inventive step of equivalents is not assessed in grant, opposition and invalidity proceedings.

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 person skilled in the art is a team consisting of an oncologist and a chemist with expertise in the formulation of pharmaceutical preparations. Lilly disputes that a chemist is part of the team, but also assumes that the average person skilled in the art has specialised pharmacological knowledge and is familiar with the search for and selection of suitable salts for a pharmaceutical preparation. A person skilled in the art with this knowledge cannot be easily distinguished from the average person skilled in the art described by the Court of Appeal. Moreover, in Lilly's own argumentation and in the expert's statements at issue by Lilly, both oncologists and chemists are used as a starting point.

no literal infringement

4.13. In so far as Lilly maintained its position that Fresenius is literally infringing the patent on appeal, that position must be rejected. Lilly itself has argued that the average person skilled in the art 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 (e.g. notice of appeal, paragraph 4.70). Lilly also did not, or at least insufficiently, dispute that the average person skilled in the art would perceive the variant of pemetrexed that Fresenius uses in its product, i.e. pemetrexed diacid with tromethamine, as a different salt form from pemetrexed disodium. Lilly itself emphasised that pemetrexed disodium and pemetrexed diacid with tromethamine are different salt forms (e.g. notice of appeal, paragraph 4.73). Its experts Frøkjær and Østergaard also state that it is clear to the average person skilled in the art that Fresenius' product deviates from the '*literal wording*' of the patent claims in this respect (Exhibit 27 of Lilly, paragraph 6.9). In view of this, it must be concluded that the average person skilled in the art will not equate pemetrexed diacid with

tromethamine with the claimed characteristic 'pemetrexed disodium', even if that characteristic is interpreted in the light of the description of the patent.

4.14. Lilly's argument that the average person skilled in the art learns from the patent document that the salt form of pemetrexed - in summary - is not relevant to the invention idea, cannot lead to a different conclusion with regard to literal infringement. That assertion is important for the assessment of the claim for 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 general professional knowledge and patent law.

question 1: technical equivalence

4.15. The problem that EP 508 seeks to solve, as the patent document makes clear in, inter alia, paragraphs [0003] to [0005] and [0016] of the description, is to reduce certain side effects of antifolates, such as pemetrexed disodium, while maintaining the therapeutic efficacy of the antifolate. The patent shows 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 person skilled in the art 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 person skilled in the art will realise that this method of claiming merely has a patent-law background, which is related to the fact that Article 53, opening words and under (c) of the EPC excludes medical treatment methods as such from patentability.

4.17. As insufficiently challenged, it is established that both the therapeutic efficacy that the patent aims to preserve and the side effects that the patent aims to reduce are caused by the pemetrexed anions and that the claimed salt form has no effect on that therapeutic efficacy and side effects of the pemetrexed anions or on the toxicity reducing properties of vitamin B12 when administered in combination with pemetrexed disodium (and optionally folic acid). Lilly supported this claim with a publication by Sierra and Goldman on the transport of folates and antifolates into the cell (Lilly Exhibit 29) and expert statements by an oncologist (statement by Professor Smit, Lilly Exhibit 26) and chemists (statement by Professor Frøkjær and Professor Østergaard, Lilly Exhibit 27). Fresenius simply argued that the properties of salts differ and that a salt form *can affect their* efficacy and toxicity. However, it has not contested that in the case of pemetrexed disodium the salt form has no effect on efficacy and toxicity.

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

> 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 above, paragraph 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 (also otherwise) pharmaceutically acceptable, i.e. suitable for use as a medicine.

4.19. It is established, as not or at least insufficiently contested, that the use of Pemetrexed Fresenius in combination with vitamin B12 and optional 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 side effects while maintaining therapeutic efficacy. It has also been established that the form in which Fresenius markets its product, i.e. pemetrexed diacid with tromethamine, performs the same function as pemetrexed disodium, i.e. merely to provide pemetrexed anions. It is not disputed 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

undisputed that the pemetrexed anions are made freely available in liquid, because pemetrexed diacid with tromethamine dissolves in it and the hydrogen particles and tromethamine groups dissociate from the pemetrexed anions (see also above at 2.30). Nor is it in dispute that pemetrexed is also pharmaceutically acceptable in this form. Fresenius has not disputed that the difference in salt form does not affect the efficacy and safety of the medicine. Lilly argued this with reference to the documents submitted by Fresenius in the context of the marketing authorisation application, which compare Lilly's and Fresenius' products and, inter alia, explicitly state 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 of Lilly) (see also above, paragraph 2.32). Fresenius also expressly acknowledges the existence of biological equivalence in these proceedings (Defence on appeal also statement of appeal in the cross-appeal, paragraph 3(e)).

4.20. Fresenius' 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 Fresenius' view, there is also 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 disputed that the hydrogen particles and tromethamine groups fulfil the same function in the product marketed by Fresenius.

4.21. Fresenius' argument that the properties of salts are very different and that not all salt forms are a suitable alternative to pemetrexed disodium can be ignored. For the assessment of the claim for equivalence, not all the properties of all the pemetrexed compounds are relevant, nor is it necessary to establish that all the 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. Nor has Fresenius indicated that pemetrexed disodium has properties relevant to the invention which Pemetrexed Fresenius does not possess. 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 Fresenius' product does not differ from the salt form mentioned in the patent claims in that respect either.

question 2: fair protection

4.22. Allowing reliance on equivalence in this case is appropriate in the light of fair 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 state of the art. The invention is disclosed in the patent document in such a way that the average person skilled in the art, with his general knowledge, 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 person skilled in the art would already arrive at the application of other pemetrexed compounds on the basis of his common general knowledge. It has been established, at least insufficiently contested, that the average person skilled in the art, on the basis of his common general knowledge, would realise 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 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, inter alia, to the material patent for pemetrexed and as such undisputed - that the average person skilled in the art knew, on the basis of his common general knowledge, that other salts of pemetrexed could be produced with the same function as pemetrexed disodium. Nor is it disputed that the selection of suitable salt forms is a routine task for the average person skilled in the art 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 person skilled in the art was able to determine routinely whether an alternative pemetrexed compound performs the function which pemetrexed disodium performs in the context of the invention.

4.24. Moreover, in addition to the specific teaching to apply pemetrexed disodium, the patent document reveals a much broader teaching which includes the application of alternative pemetrexed compounds. For instance, the patent document expressly teaches the person skilled in the art 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 document). Among other things, this section teaches the average person skilled in the art 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 document therefore also puts the average person skilled in the art on the trail of looking for alternatives to pemetrexed disodium. As considered above, the average person skilled in the art would routinely arrive at alternative pemetrexed compounds that function in the same way.

4.25. Fresenius' argument that the average person skilled in the art cannot predict the properties of a salt or acid prior to routine experimental research does not lead to a different outcome. As both parties pointed out with reference to the UK High Court's ruling in the pemetrexed case,5 this unpredictability does not alter the fact that the average person skilled in the art would have 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 person skilled in the art from looking for an alternative pemetrexed compound.

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

4.27. Fresenius's argument that it was granted a patent for the development its formulation cannot lead to a different outcome. The fact that a product contains a measure which is inventive in relation to the patent document does not preclude that product from also applying the teaching of the patent and that it is therefore fair towards the patent proprietor to bring the product in question within the scope of protection of the patent. The inventive step may in fact take the form of a complementary teaching, in the form of the addition of a measure to the patented product or the selection of a specific form of implementation of the general teaching of the patent. That is also the situation in this case. Lilly noted undisputedly (i) that Fresenius' patent does not concern pemextrexed diacid with tromethamine as such, but pemetrexed diacid with tromethamine in a special 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 grant procedure that pemetrexed diacid with tromethamine as such was the obvious choice. This opinion of the EPO is supported by the fact that tromethamine, as Lilly has substantiated and stated uncontested, was a well-known buffering agent/H-regulator in 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. It will be clear to the average person skilled in the art, when reading the claims in the light of the description, that the claims leave room for equivalents as far as the salt form is concerned. He will realise that the patent's teaching on this point is clearly broader than the wording of those claims and that there is no good justification for limiting the scope of protection to the application of the pemetrexed disodium mentioned in the claims.

4.29. As considered above, the patent document explicitly discloses a teaching that includes the application of alternative pemetrexed compounds, namely that the side effects of an antifolate can be reduced by administration in combination with vitamin B12 (and optionally folic acid). Moreover, this teaching is in line with the knowledge with which the average person skilled in the art reads the patent document, including the knowledge that the pemetrexed anions are responsible for the therapeutic efficacy and side effects 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 person skilled in the art who reads the patent with his common general knowledge, the teaching of the patent is therefore clearly

broader than the wording 'pemetrexed disodium' of the claims. In other words, it is clear to the average person skilled in the art that he also makes use of the inventive concept behind the words of the claims when applying alternative pemetrexed compounds.

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

4.31. The patent document does not contain a valid ground for limiting the scope of protection to the application of pemetrexed disodium. The patent document 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 stability, solubility or absorption. The only thing the patent document learns on pemetrexed disodium is that Lilly produces pemetrexed in that salt form, i.e. that pemetrexed disodium is available. The average person skilled in the art 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. The average person skilled in the art knows from his common general knowledge that and how other salts of pemetrexed could be developed that will have the same effect.

4.32. Contrary to Fresenius' opinion, the fact that the patent in the claims and description only mentions pemetrexed disodium, without the addition of a clause such as '*or other pharmaceutically acceptable salts*', does not provide a valid grounds to limit the scope of protection to pemetrexed disodium. Recourse to equivalence would become impossible if that mere fact were to constitute a valid ground to limit the scope of protection to a product with that feature. That result would run counter to the rule that equivalence must be taken into account in an appropriate manner.

4.33. Nor does the fact that the patent document explicitly mentions alternatives for other features in the claims and the description, as in the case of vitamin B12 '*pharmaceutical derivatives thereof*', provide a valid ground to limit the scope of protection. It cannot be inferred from that fact *a contrario* that in the case of pemetrexed disodium equivalents are excluded from the scope of protection.

4.34. Finally, Fresenius referred to paragraph [0016] of the description, 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, too, does not provide good grounds for limiting the scope of protection. On the contrary, inter alia this passages expressly teaches the person skilled in the art that the invention is *not* limited to pemetrexed disodium (see above, 4.24).

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

4.36. Fresenius rightly noted that the average person skilled in the art 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 can fulfil the functions of pemetrexed disodium in the context of the invention. It is conceivable, for example, that the solubility of a certain 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 perform the functions of pemetrexed disodium in the context of the invention. However, this does not imply that there is a valid reason to exclude from the scope of protection of EP 508 the use of alternative pemetrexed compounds which do perform the same functions in the context of the invention, such as pemetrexed diacid with tromethamine.

4.37. The average person skilled in the art will also know on the basis of his common general knowledge that the selection of an alternative pemetrexed connection requires research, the results of which cannot be predicted in advance. However, the person skilled in the art also knows how to carry out this research and that he has a reasonable chance of success that he will find a suitable alternative

with this research. The need for such research therefore does not provide a valid ground for limiting the scope of protection of the claims to pemetrexed disodium.

4.38. The fact that Lilly expresses a preference for pemetrexed disodium in the material patent (EP 0 432 677) and for a heptahydrate form of pemetrexed disodium in another patent (EP 1 259 513 B1) cannot lead to a different judgement. It has not been asserted or demonstrated that the beneficial properties which Lilly attributed to (a specific form of) pemetrexed disodium in the context of those patents were part of the common general knowledge. Moreover, Fresenius did not claim that the average person skilled in the art would consider that, without those properties, pemetrexed compounds could not perform the function that pemetrexed disodium performs in the context of the invention. Fresenius did not sufficiently explain why the average person skilled in the art would see the properties of (a specific form of) pemetrexed disodium as a valid reason for limiting the scope of protection to pemetrexed disodium.

4.39. The fact that Lilly explicitly revealed and claimed other acids and salts in another patent (EP 1 265 612 B1) cannot lead to a different interpretation either. It cannot be deduced *a contrario* that the scope of protection of EP 508 should be limited to pemetrexed disodium.

4.40. On the basis of the above, it must be concluded that it will be clear to the average person skilled in the art, reading 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 an examination of the prosecution history file for this purpose. If the average person skilled in the art did consult the prosecution history, he would not arrive at a different opinion, because it does also not contain a valid reason for limiting the scope of protection to the application of pemetrexed disodium. On the contrary, as will be explained below, examination of the prosecution history would strengthen the average person skilled in the art in his opinion that the scope of protection is not limited to the application of pemetrexed disodium.

4.41. As Fresenius himself noted, the use of the characteristic pemetrexed disodium can be traced back to the original application, in which pemetrexed disodium was the only described form of pemetrexed (see 2.21). A good reason to limit the scope of protection to that salt form cannot be deduced from this. On the contrary, the conclusions of the original application were much broader and included - in summary - the application of *each* antifolate in combination with a *methylmalonic acid lowering agent* (such as vitamin B12). Those conclusions also included pemetrexed compounds other than pemetrexed disodium.

4.42. The average person skilled in the art will not see good grounds for limiting the scope of protection to the application of pemetrexed disodium. On the contrary, the granting history confirms that Lilly intended a broader scope of protection which also includes the application of other salts and acids of pemetrexed. Indeed, after the EPO's research department argued that the broad claim was not new in the light of two publications on the use of vitamin B12 in combination with antifolates other than pemetrexed, Lilly put forward a conclusion concerning - in summary - the use of 'pemetrexed' in combination with vitamin B12 (see paragraphs 2.17, 2.18 and 2.19 above). This conclusion also clearly includes pemetrexed compounds other than pemetrexed disodium.

4.43. Examination of the grant file shows the average person skilled in the art that the characteristic 'pemetrexed disodium' was subsequently introduced as a result of an objection by the research department of the European Patent Office based on Article 123(2) of the EPC against the concept of 'pemetrexed' (see 2.20). A limitation of the claims on that ground does not preclude a claim for equivalence. It can only be deduced from that restriction that Lilly wished to ensure that the subject matter of its patent was covered by the content of the original application. A good ground for limiting the scope of protection to the application of pemetrexed disodium and the exclusion of equivalents cannot be read therein. The successful application of equivalence in the context of determining the scope of protection does not require that the equivalents be covered by the content of the original application. The rule set out in Article 123(2) of the EPC, as Fresenius also acknowledges (Conclusion in reply, paragraph 84 and Statement in reply, paragraph 167), does not apply when determining the scope of protection of a patent. Added matter and scope of protection are separate issues.

4.44. Fresenius' reliance on the ratio of Article 123(2) EPC cannot lead to a different judgement. Fresenius argues that that provision protects the legal certainty of third parties and ensures that the scope of the patent is proportionate to the contribution of the patent proprietor to the state of the art. It

follows from the foregoing that those two points of view are also taken into account in the assessment of the claim for equivalence. Analogous application of Article 123(2) EPC is not necessary for this purpose.

4.45. There are also legitimate reasons not to apply the requirements of Article 123(2) EPC when assessing a claim for equivalence in the context of determining the scope of protection of a patent. Indeed, there are substantial differences between, on the one hand, adding equivalents to the patent claims and the description, which is covered by Article 123(2) of the EPC, and, on the other hand, taking account of equivalents in the context of determining the scope of protection of the patent, which is covered by Article 69 of the EPC and the Protocol.

> 4.45.1. Firstly, adding equivalents to the patent claims and the description may have a greater impact on the scope of protection. Indeed, the scope of protection of the patent is determined by the claims in the light of the description as it reads after the addition of the equivalents. That scope of protection may, in circumstances subsequent to the amendment, include equivalents of the equivalents added. That possibility does not arise where equivalents are invoked. Under those circumstances, equivalents may be included in the scope of protection, but not equivalents of equivalents.
>
> 4.45.2. Secondly, the addition of an equivalent through an amendment of the patent notation may have an effect on the novelty, inventive step and sufficiency of the patent in the sense that the patent derives novelty, inventive step or sufficiency in whole or in part from the added equivalent. This would confer an unjustified advantage on the applicant, since novelty, inventive step and after-effectiveness would be assessed on the date of application, whereas at that date the equivalent was not yet part of the invention disclosed in the original application. That effect does not arise where equivalence is invoked to determine the scope of protection. Indeed, equivalents are not taken into account when assessing novelty and inventive step, nor can they remedy a lack of practicability.
>
> Because of these differences, Article 123(2) of the EPC imposes relatively strict requirements on the addition of matter to the patent document which should not be applied (by analogy) when determining the scope of protection of a patent.

4.46. The circumstances mentioned by Fresenius, such as that Lilly did not enter into discussion with the EPO on the objection based on Article 123(2) EPC, that Lilly is a pharmaceutical superpower that has deliberately opted for the restriction to the application of pemetrexed disodium, that Lilly did not file a divisional application and that Lilly could have formulated the patent claims in other ways, cannot lead to a different judgment. Those circumstances are without prejudice to the fact that the average person skilled in the art will conclude from the grant file that Lilly introduced the words pemetrexed disodium in response to the added-matter objection and that the average person skilled in the art will not derive good grounds for limiting the scope of protection to the application of pemetrexed disodium.

4.47. The above would possibly be different if the average person skilled in the art were to assume that added matter was not a real problem and that there must therefore be another reason for introducing the terms pemetrexed disodium in the conclusions. Fresenius - rightly - did not say that. Fresenius does not claim that there would have been no added matter if Lilly had proposed a conclusion that included other pemetrexed compounds, let alone that the average person skilled in the art would have realised this. Fresenius merely argued that Lilly had a reasonable chance of succeeding in overcoming the research department's objection. That is insufficient to assume that the average person skilled in the art would think that there was another reason for introducing the wording, let alone that there is another reason that provides good grounds for limiting the scope of protection.

4.48. Fresenius' argument that the average person skilled in the art would deduce from the patent and the grant file that the use of the term 'pemetrexed disodium' in the claims and description was a conscious choice or a not clearly unintentional choice by Lilly, cannot lead to a different conclusion. In so far as Fresenius refers to Lilly's subjective will or intention, the argument can be disregarded because the subjective will or intention of the applicant does not play a decisive role in determining the scope of protection of a patent. In so far as Fresenius takes account of what the average person skilled in the art objectively draws from the patent specification and the grant file, the arguments coincide with

her defence against Lilly's assertion that there are no good grounds for limiting the scope of protection to the application of pemetrexed disodium. That defence has already been rejected.

4.49. Moreover, on the basis of the grant file, the average person skilled in the art will find that the use of the term 'pemetrexed disodium' in the claims has its origins in an unfortunate formulation of the application, in which Lilly did not, or at least did not provide a clear basis for a claim that is midway between, on the one hand, a claim formulated too broadly (in view of the state of the art) that includes all antipholates and, on the other hand, a claim formulated too narrowly (in view of the contribution of the patent to the state of the art) that only mentions pemetrexed disodium. The use of that wording in the original application cannot be regarded as a deliberate or manifestly unintentional choice by Lilly to limit the scope of protection of the patent to the application of pemetrexed disodium. On the contrary, it is obvious to the average person skilled in the art that those terms were *not* intended to limit the scope of protection. It is therefore clear to the average person skilled in the art who learns from the grant file that that is the background to the use of the term pemetrexed disodium in the claims of the patent as granted, that Lilly has never chosen 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 should always prevail if an equivalent *could have been* expressly claimed with careful wording of the original application and the patent notice, that argument must be rejected. Such a view goes too far in general and ignores the fact that, when determining the scope of protection of a patent, account must be taken of reasonable legal certainty for third parties and equitable protection for the patent proprietor.

4.51. The opinion of the District Court that Lilly did not state that there was an unintentional error or omission in the original application, that Lilly himself believes that the original application does provide a basis for a broader conclusion and that Lilly did not state that the average person skilled in the art would understand that there is no basis for the broader conclusion, must be dismissed. In any event, on appeal, Lilly expressly took the position that the original application does not provide a basis for broader conclusions, that the average person skilled in the art will see this and that (in retrospect) it would have been better if the original application had mentioned '*pemetrexed and pharmaceutically acceptable salts thereof*'.

4.52. The fact that Lilly pemetrexed disodium was referred to in the patent application as the '*most preferred*' form of implementation is not a good ground for limiting the scope of protection to pemetrexed disodium. That application did not contain any pemetrexed compounds other than pemetrexed disodium, but only other antifolates. The fact that the application of pemetrexed disodium is preferable to other antifolates such as methotrexate and Lometrexol will not lead the average person skilled in the art to conclude that pemetrexed disodium also has advantages over other pemetrexed compounds.

4.53. Finally, Fresenius pointed out that Lilly's patent attorney in his letter of 8 March 2006 to the research division states 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 remark the average person skilled in the art will not see good grounds for limiting the scope of protection to the application of pemetrexed disodium to the exclusion of other pemetrexed compounds. Indeed, the average person skilled in the art studying the grant file will see that the distinction to which the patent attorney refers has not been introduced in the context of the amendment of the claims from pemetrexed to pemetrexed disodium. The distinction was already part of the amended description submitted by Lilly in a letter dated 23 December 2004 in the context of the amendment of the claims from all antifolates to pemetrexed. In the light of this, it must be assumed that the distinction relates to the application of antifolates in general versus the application of the antifolate pemetrexed. The reason why the authorised representative highlights the distinction in his letter of 8 March 2006 is, as he explains in the letter, that the passages on '*subject matter to which the present invention generally relates*' should be retained in the description because they make it clear that the reduction in toxicity of the antifolate when using the combination therapy is relevant to the invention. From this the average person skilled in the art will not deduce that the scope of protection is limited to pemetrexed disodium to the exclusion of other pemetrexed compounds.

question 4: novelty and inventiveness

4.54. Fresenius has not contested - apart from the validity defence to be discussed below - that its product is new and inventive in relation to the state of the art of the patent as referred to in paragraph 4.11 of this judgment. The Court can therefore take that as a basis.

conclusion on the scope of protection

4.55. On the basis of the above, it must be concluded that Lilly's grievance against the District Court's finding that it took due account of equivalents is successful. Once again, it must be held that Fresenius' product falls within the scope of protection of, inter alia, Clause 2 of EP 508. The other grievances that Lilly put forward in principal appeal and Fresenius in incidental appeal against the assessment of the scope of protection by the District Court have been taken into account in the previous assessment by the Court of Appeal and can remain unanswered.

4.56. The Court's judgment on the scope of protection of EP 508 is in line with the judgments of the highest foreign courts on the scope of protection of the foreign parts of EP 508. Therefore, the Court does not need to further explain how its judgment relates to those rulings.

4.57. The Court therefore falls to the assessment of Fresenius' incidental ground 6 about the validity of, among other things, conclusion 2 of EP 508, which Fresenius put forward under the condition that the Court concludes that her product falls within the scope of protection of EP 508.

validity conclusion 2

4.58. Fresenius' argument that the invention claimed in Clause 2 of EP 508 results from the state of the art in a way that is obvious to the average person skilled in the art, must be rejected for the following reasons.

4.59. Fresenius argues that the claimed invention lacks inventive step because:
a. the general expertise was to use antifolates, including pemetrexed disodium
use in combination with folic acid to reduce the toxicity of the antifolate
without prejudice to the effectiveness of the antifolate;
b. it was also general knowledge that there was a link between folate and
vitamin B12 in the metabolism of a cell, more specifically that by means of vitamin B12 the folate contained in the so-called 'folate trap' can be made free and becomes available as functional folate;
c. for this reason alone it was obvious to the person skilled in the art to try out successfully, with reasonable expectation, whether a deficiency in functional folate can be solved by administering vitamin B12;
d. the move to vitamin B12 was once again obvious now that it was known that
cancer patients (who are often already of age) often had a vitamin B12 deficiency;
e. moreover, there was no prejudice against the use of vitamin B12 in the cancer treatment.

These theses will be discussed in turn below. Partly in view of what has been considered above about the limited importance of the salt form, pemetrexed disodium will be referred to as pemetrexed for short.

use antifolates in combination with folic acid

4.60. Fresenius' thesis that it was general practice to use antifolates, including pemetrexed, in combination with folic acid to reduce the toxicity of the antifolate without compromising the effectiveness of the antifolate must be rejected.

4.61. Against this, Lilly argued that the average person skilled in the art did *not* combine antifolates with folic acid on the basis of his general professional knowledge, because he expected the administration of folic acid to undermine the effect of the antifolate. Lilly pointed out that the average person skilled in the art would realise on the basis of his general professional knowledge that antifolates and folic acid (synthetic folate) counteract each other's efficacy because they are in a

competitive relationship with each other. Lilly substantiated this with expert statements (statement O'Dwyer, exhibit 60 of Lilly, and statement Chabner, exhibit 71 of Lilly), a handbook for clinicians which states that folic acid can inhibit the action of methotrexate - one of the two antifolates marketed in Europe (Lilly exhibits 68-70) - and the SmPC of the antifolate raltitrexed - the other antifolate marketed in Europe - which explicitly states that folic acid should not be administered in combination with the antifolate because it can affect its action (exhibit 58.4 of Lilly).

4.62. The fact that the average person skilled in the art knew that antifolates and folic acid are in a competitive relationship is not in dispute as such. Fresenius himself has argued that antifolates and folates administered via folic acid can both bind to enzymes that play a role in cell division 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. She has not disputed that this is part of the general professional knowledge of the average person skilled in the art.

4.63. Fresenius also does not substantiate its claim with examples of folic acid antifolate combination therapies used for cancer treatment in clinical practice at the priority date. On the contrary, if not, or at least insufficiently contested, it is established that such combination therapies were not used on the priority date. Fresenius did, however, refer to a patent application by Vesta (exhibit 52 of Fresenius) and a publication by Carrasco (exhibit 51 of Fresenius). However, these documents do not reveal any combination therapy of an antifolate with folic acid to treat cancer. The documents describe the administration of, among other things, folic acid to treat (the effects of) increased homocycsteine and acute megaloblastic anaemia (a particular form of anaemia). The fact that the publications also mention that these syndromes may be the result of previous administration of the antifolate methotrexate does not mean that they reveal a combination treatment within the meaning of the patent, let alone that the combination with folic acid does not impair the effectiveness of the antifolate.

4.64. Fresenius also does not substantiate her thesis with publications on clinical research into the combination of antifolates with folic acid. Fresenius does point to publications on clinical phase I research into the combination of folic acid and antifolates such as pemetrexed (two abstracts by Hammond, exhibit 39 and 40 by Fresenius). However, Fresenius himself has emphasised that 'nothing' can be concluded from this research about the efficacy of the antifolate, because Phase I clinical trials are aimed at establishing the safety, maximum dose and pharmacokinetics of the drug, rather than its efficacy, and because the small number of participants in the trial had already had many other treatments. The results of this research cannot therefore serve to support Fresenius' assertion that the general expertise was that folic acid administration does not reduce the effectiveness of an antifolate.

4.65. Fresenius bases her thesis mainly on several publications describing the results of a pre-clinical study on the administration of the combination of pemetrexed and folic acid in mice (Jackman, exhibit 32 of Fresenius, and the abstract and article by Worzalla, exhibits 37 and 38 of Fresenius, and Cripps, exhibit 35 of Fresenius). However, preclinical results are insufficient to support Fresenius' thesis that it was general professional knowledge to use antifolates in combination with folic acid without compromising the effectiveness of the antifolate, especially in the light of the above mentioned knowledge of the average person skilled in the art about the competitive relationship between antifolates and folic acid. It may be general professional knowledge that the results of a pre-clinical study 'suggest' beneficial effects of folic acid administration, as Jackman quoted by Fresenius puts it, but that is not the same as general professional knowledge that these effects exist.

4.66. In addition, the published pre-clinical studies show that when folic acid was administered, pemetrexed at much higher doses had to be administered to mice to achieve the same effect. The publications show that tumour growth was already completely inhibited at a dose of 0.3 mg/kg in mice that were not given folic acid. In mice that did receive folic acid, that effect was only achieved at a 100-fold higher dose of 30 mg/kg. Partly in view of the average person skilled in the art's knowledge of the competitive relationship between folates and antifolates, the average person skilled in the art would not assume, on the basis of these results, that the effect of pemetrexed is maintained when folic acid is administered without further investigation.

4.67. Fresenius' argument that the preclinical research results (and the results of phase I clinical trials) also indicate that folic acid reduces certain side-effects of pemetrexed and that, therefore, the administration of pemetrexed in higher doses should be disregarded. The fact remains that the pre-clinical research results only suggest that the effects of pemetrexed are maintained at those high doses

and that the results of the Phase I clinical trial do not help the average professional in this respect, according to Fresenius. In addition, Lilly has not argued, or at least has not contested sufficiently, that the mouse experiment used, with cancer cells specifically designed to be sensitive to pemetrexed, has poor predictive value for the relationship between toxicity and efficacy. Therefore, the fact that the research results of the mouse experiment suggest that at high doses of pemetrexed in combination with folic acid, certain side effects of pemetrexed have been reduced and the action of pemetrexed on the specific cancer cells has been maintained does not mean that the average person skilled in the art would assume, without further research, that this will also be the case with ordinary cancer cells.

4.68. Fresenius' argument that on the basis of the preclinical research results referred to (and the results of phase I clinical research) it was obvious to the average person skilled in the art to investigate further whether the administration of folic acid would reduce the side-effects of pemetrexed without detracting from the efficacy of pemetrexed could be ignored. After all, the invention claimed by Lilly in EP 508 does not concern the combination of pemetrexed with folic acid alone. Contrary to Fresenius' view, the fact that the US and Japanese courts, inter alia, found a patent claim which did relate to the combination of pemetrexed with folic acid only to be non-inventive is therefore not relevant to the assessment of the validity of EP 508.

4.69. In addition, Fresenius bases its knowledge on the use of the combination of antifolates and folic acid on Grindey's US patent application (US 5 217 974, exhibit 78 of Lilly), which proposes a mechanism for reducing the toxicity of a specific type of antifolate (including Lometrexol) by pretreatment with a certain type of egg white binding agent (such as folic acid). Apart from the fact that a single patent application is insufficient to substantiate the general professional knowledge required, it must be assumed that the doctrine of this patent application was obsolete at the priority date. Lilly drew attention to Laohavinij's subsequent publication (Annex 3 to exhibit 58 of Lilly), which describes a much more extensive clinical study on the combination of Lometrexol and folic acid (Laohavinij's study is a clinical study with 43 patients while Grindey contains data from only one patient). In line with Lilly's scepticism about the effect of folic acid, Laohavinij explicitly mentions the concern that the administration of folic acid will bypass the action of the antifolate or even support tumour growth. The results of her research do not remove this concern. Laohavinij describes that, in general, the clinical response of Lometrexol alone was not observed when Lometrexol was administered in combination with folic acid. When folic acid was administered, only one patient was found to show a partial response.

4.70. Finally, Fresenius seems to want to substantiate the alleged knowledge about the combination of antifolates and folic acid by stating that the average professional knew that tumour cells are fast dividing cells that need more folic acid than healthy cells. That statement must be rejected. Lilly has disputed it, substantiating it with statements by experts. Among other things, Lilly pointed out that there are also healthy fast dividing cells, such as those in the bone marrow and gastrointestinal tract, and that antifolates do not distinguish between healthy cells and cancer cells. Fresenius also only substantiated the thesis with a quote from chapter 12 of Jackman's collection, which suggests the administration of folic acid as a measure that could ('*may*') normalise the response by restoring folate pools in tissue with low folate requirements. Jackman did not substantiate this suggestion with research results. Furthermore, the suggestion is made in a chapter on the antifolate Lometrexol and LY309887. As noted above, the average person skilled in the art knew on the priority date that clinical research into the combination of Lometrexol with folic acid did not support the suggestion made in Jackman.

cohesion folate and vitamin B12 and folate trap

4.71. In the middle can remain whether the knowledge described by Fresenius about the relationship between folate and vitamin B12 belongs to the general knowledge. If this is not the case the inventive step should be stranded there already, because Fresenius did not explain why the average person skilled in the art would consult information about the relationship between folate and vitamin B12 and the folate attack. Insofar as this knowledge does belong to general professional knowledge, this cannot lead to the opinion that the claimed invention lacks inventive step. On the basis of this knowledge it is not obvious for the average person skilled in the art to investigate, with a reasonable expectation of success, whether a deficiency in functional folate can be solved by the administration of vitamin B12.

4.72. Contrary to what Fresenius suggests, it does not follow from the publications quoted by Fresenius in support of the alleged knowledge about the relationship between folate and vitamin B12 (Baynes,

exhibit 33 of Fresenius, and Scott, exhibit 34 of Fresenius) that there is a problematic deficiency of functional folate in the treatment of cancer with pemetrexed, nor that the administration of vitamin B12 always leads to a deficiency of functional folate being resolved. Baynes and Scott's publications describe that vitamin B12 deficiency results in folate (5-methyl-tetrahydrofolate or 5-MTHF) not being converted into functional folate (tetrahydrofolate or THF). The average person skilled in the art learns from this that the administration of vitamin B12 has an effect on the amount of functional folate *if* there is a deficiency of vitamin B12. Based on this knowledge, the average person skilled in the art would therefore only expect an effect of vitamin B12 administration in patients with a vitamin B12 deficiency.

4.73. An indication that patients administered pemetrexed have a deficiency of functional folate or a deficiency of vitamin B12 does not come from Baynes and Scott. Indeed, they do not present the information on the relationship between folate and vitamin B12 in the context of cancer treatment. They describe the relationship between folate and vitamin B12 in the context of haematological abnormalities, such as megaloblastic anaemia and pernicious anaemia (forms of anaemia), and neuropathy (nerve damage). This means that the average person skilled in the art on the basis of these publications only has reason to assume that there is a deficiency of functional folate and to investigate whether this deficiency is caused by a deficiency of vitamin B12 when the haematological abnormalities and neuropathy described occur. In the treatment of cancer with pemetrexed, the average person skilled in the art has no reason, based on these publications, to assume that there is a deficiency of functional folate that needs to be remedied. On the contrary, the average person skilled in the art knew that the therapeutic effect of antifolates such as pemetrexed is based on the competitive relationship between antifolates and folates and that, in this sense, treatment with an antifolate is aimed precisely at creating a deficiency in functional folate (see 4.62). In addition, on the basis of these publications the average person skilled in the art has no reason to investigate whether the side effects of pemetrexed are caused by any deficiency of vitamin B12. After all, it follows from the fact that these side effects are caused by administration of the antifolate pemetrexed and Lilly arguably argued that the average person skilled in the art knew that pemetrexed intervenes in the DNA cycle instead of the cycle in which vitamin B12 plays a role.

4.74. If, in spite of the above, the average person skilled in the art had checked whether patients who were administered pemetrexed were deficient in vitamin B12, he would have come across the publications of Niyikiza (Appendix 11, at exhibit 58 of Lilly) and Zervos (Appendix 12, at exhibit 58 of Lilly). Both publications teach the average person skilled in the art that no correlation has been observed between the specific biomarker for the status of vitamin B12 (methyl malonic acid or MMA) and the toxicity of pemetrexed. No other publications have been found to show a correlation between the status of vitamin B12 and the toxicity of pemetrexed. In the light of this, it cannot be assumed as certain that the average person skilled in the art would expect that patients who were administered pemetrexed had a deficiency of vitamin B12 (see also section 4.84 below on the alleged deficiency of vitamin B12 in cancer patients in general).

4.75. In addition, the haematological context in which the relationship between folate and vitamin B12 is presented means that knowledge of this relationship does not teach the average person skilled in the art anything about the effect of vitamin B12 administration on the side effects and therapeutic efficacy of pemetrexed. Fresenius' comment that Baynes does discuss the treatment of cancer with antifolates and DNA synthesis in other places in his book does not make this any different. Those passages do not refer to the relationship between folates and vitamin B12, and vice versa the passage describing the relationship between folates and vitamin B12 does not refer to the passages on the treatment of cancer with antifolates.

4.76. If the average person skilled in the art were to assume that the administration of vitamin B12 leads to an increase in functional folate and make a link between the increase in functional folate and the side effects and therapeutic efficacy of pemetrexed, this would not lead him to the solution of the objective problem. Lilly argued that the average person skilled in the art would expect the alleged increase in functional folate to undermine the therapeutic efficacy of pemetrexed. In this context, Lilly referred to the average person skilled in the art - described above and as such undisputed - knowledge of the competitive relationship between folates and antifolates. The fact that the average person skilled in the art did not have a reasonable expectation of maintaining the efficacy of pemetrexed is further supported by the expert statements submitted by Lilly (Chabner, exhibit 71, O'Dwyer, exhibit 64 and Calvert, exhibit 58), all of which state that they would have expected the opposite on the priority date,

and publications belonging to the state of the art that teach that administration of vitamin B12 stimulates the growth of tumours (Vidal, exhibit 5 of Lilly, and McLean, exhibit 76 of Lilly).

4.77. Fresenius did not argue that the average person skilled in the art would consider that the administration of vitamin B12 would have the same effect on the side effects and therapeutic efficacy of pemetrexed as the administration of folic acid and that therefore, on the basis of the results of the pre-clinical study referred to above with the combination of folic acid and pemetrexed, the average person skilled in the art would reasonably expect the administration of vitamin B12 to reduce the side effects of pemetrexed while maintaining its therapeutic efficacy. To the extent that Fresenius intended to argue that the average person skilled in the art would expect this on the basis of the described combination of folate and vitamin B12, that claim must be rejected in the absence of any explanation and justification, also in the light of what Lilly argued about the differences between folic acid and vitamin B12.

4.78. Firstly, Lilly has undisputedly argued that folate administered via folic acid is a substrate in the folate metabolism, i.e. a substance which is ingested, whereas vitamin B12 is a cofactor in that process, i.e. a substance which is not ingested and is therefore used over and over again. In the light of this, it cannot be assumed that the average person skilled in the art will simply believe that the administration of vitamin B12 has the same effect on the exhibit 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 has argued that folic acid can bypass the folate trap. When folic acid is administered in high concentrations, Lilly said that the folate will enter the cell in an inactive form and keep the DNA cycle, which is responsible for the side effects and therapeutic action of pemetrexed, going. Even on this basis, it cannot be assumed that the average person skilled in the art will believe that the administration of vitamin B12 has the same effect on the exhibit 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 alleged circumvention of the folate trap with various expert statements and a reference to Scott's handbook submitted by Fresenius himself, which explicitly describes that process (exhibit 34 of Fresenius). Fresenius and its expert Molloy do not appear to dispute that the folate trap is circumvented when high concentrations of folic acid are administered. Molloy's statement identifies the bypass described by Scott as "*a situation that could occur where large doses of folic acid are ingested*" and calls it "*biologically plausible*" that it works by ingressing *folic acid* into the cell and participating in the DNA cycle (Molloy statement, Fresenius exhibit 50, page 5). Fresenius does deny that cancer patients are given high doses of folic acid. That objection alone cannot succeed because clinical trials of the combination of pemetrexed and folic acid have used doses of 3 mg or more, while, according to Scott, the circumvention already occurs at doses of 1 mg.

4.81. In addition, as noted above, the results of the pre-clinical study of the combination of pemetrexed with folic acid do not teach the average person skilled in the art that administration of folic acid reduces the side effects of pemetrexed and preserves its therapeutic efficacy. That uncertainty about the maintenance of the efficacy of pemetrexed in the administration of folic acid and the uncertainty described above about the effects of vitamin B12 administration compared to the effects of folic acid administration, taken together, mean that it cannot be maintained that it was obvious to the average person skilled in the art to investigate with a reasonable expectation of success whether administration of vitamin B12 reduces the side effects of pemetrexed without compromising the therapeutic efficacy of pemetrexed.

4.82. In itself, Fresenius rightly argued that when answering the question of whether the average person skilled in the art would investigate the administration of vitamin B12, the extent of the possible 'reward' should be taken into account. Contrary to what Fresenius argues, however, in this case that factor does not unambiguously support Fresenius' position on the inventiveness of the invention claimed in Clause 2. It is true that the reward for successful cancer treatment is great, but Lilly has argued, and undisputedly noted, that on the priority date it was known that clinical studies had shown that the toxicity of pemetrexed - without vitamin B12 and folic acid - was tolerable and controllable (it was only after that date that studies were published which revealed that pemetrexed did have very serious side effects). Assuming that the average person skilled in the art assumed that the side effects of pemetrexed were reasonably under control, the average person skilled in the art would have thought

that he had relatively little to gain from a drug that further reduces the side effects and it must be assumed that his concerns about the preservation of the effects of pemetrexed weighed relatively heavily.

4.83. The fact that it was not obvious for the average person skilled in the art to add vitamin B12 to a cancer treatment with the combination of an antifolate and folic acid is confirmed by the parties' agreement that vitamin B12 was not administered in any of the clinical trials conducted with the combination of an antifolate and folic acid on the priority date. The documents Grindey (exhibit 78 of Lilly), Laohavinij (annex 3 to exhibit 58 of Lilly), Rees (annex 5 to exhibit 58 of Lilly), Hammond (exhibits 39 and 40 of Fresenius) describing those studies also do not suggest the use of vitamin B12. Vesta (exhibit 52 of Fresenius) and Carrasco (exhibit 51 of Fresenius) do describe administration of a combination of folic acid and vitamin B12, but in the cases described in these publications, these vitamins were not administered in combination with the antifolate (see 4.63).

vitamin B12 deficiency

4.84. Fresenius' thesis that 15 to 20% of cancer patients in general are known to be deficient in vitamin B12 cannot lead to a different judgement. As established above, the average person skilled in the art knows that this deficiency is not the cause of the side effects of pemetrexed, supported by publications that reveal no correlation between the status of vitamin B12 and the toxicity of pemetrexed, and the average person skilled in the art would not reasonably expect vitamin B12 administration to reduce the side effects of pemetrexed without impairing the therapeutic efficacy of pemetrexed. The average person skilled in the art would therefore not opt for a combination of pemetrexed with vitamin B12 in the context of cancer treatment.

4.85. Fresenius' thesis that a deficiency of vitamin B12 can eventually lead to haematological abnormalities such as neutropenia does not change this. This fact does not make it obvious for the average person skilled in the art to make the administration of vitamin B12 part of the treatment of cancer with pemetrexed if a vitamin B12 deficiency is found. On the contrary, because of the possible interaction with the antifolate, it is obvious to separate the treatment of the haematological abnormalities in question from the treatment with pemetrexed. This can be done, on the one hand, by prioritising the generally urgent need for pemetrexed cancer treatment over the treatment of the health problems caused by vitamin B12 deficiency. On the other hand, in the event of serious health problems due to vitamin B12 deficiency, it may be concluded that the patient is not healthy enough to undergo treatment with pemetrexed, in which case the administration of a combination of folic acid and pemetrexed will not be necessary either. The expert statements submitted by Lilly support the view that these two options, and not the combination therapy of pemetrexed and vitamin B12, would be obvious to the average person skilled in the art in the event of a suspected vitamin B12 deficiency.

no bias

4.86. Fresenius' argument that there was no prejudice against the use of vitamin B12 in cancer treatment can be ignored. The assertion that there was no prejudice against the use of vitamin B12 is insufficient to combat the inventiveness of the claimed invention.

4.87. The opinion given above on the inventive step of the invention claimed in claim 2 of EP 508 is also not based on overcoming a prejudice. However, the scepticism expressed by Lilly regarding the maintenance of the efficacy of pemetrexed when vitamin B12 and/or folic acid were administered was taken into account in the assessment of, among other things, Fresenius' thesis that the average person skilled in the art was known to administer antifolates in combination with folic acid with a view to reduce the toxicity of the antifolate without compromising the effectiveness of the antifolate and Fresenius' thesis that it was obvious to try, with a reasonable expectation of success, whether a deficiency of functional folate could be resolved by the administration of vitamin B12. This scepticism was also well-founded by Lilly's uncontested knowledge of the competitive relationship between folates and antifolates, expert opinions and state-of-the-art documents.

problem-solution approach

4.88. In addition to the argumentation described in 4.59, Fresenius put forward an attack based on the *problem-solution approach on the* inventiveness of the invention claimed in claim 2. This reasoning, too, cannot lead to the conclusion that the invention is not inventive.

4.89. It remains to be seen whether Chapter 8 of Jackman's collection of *Antifolate Drugs in Cancer Therapy* (exhibit 32 by Fresenius, hereafter Jackman), in the light of the scepticism of the average person skilled in the art about the effect of administering folic acid discussed above, can be regarded as the closest state of the art, i.e. a realistic starting point for assessing inventiveness. If this is assumed to be the case with Fresenius, this cannot lead to the assessment of the invention claimed in claim 2 not being inventive, for the following reasons.

4.90. Jackman's Chapter 8 describes, among other things, the pre-clinical research on the combination of pemetrexed with folic acid in mice discussed above. The (main) difference with the invention claimed in conclusion EP 508 is the use of vitamin B12 or a pharmaceutically acceptable derivative thereof. It is not disputed that the effect of this additional measure is to reduce the toxic side effects of pemetrexed while maintaining the therapeutic efficacy of pemetrexed. On this basis, the objective problem which the invention claimed in Conclusion 2 solves must be formulated as a reduction in the toxic side-effects of pemetrexed while maintaining its therapeutic efficacy. Fresenius also takes that as its starting point.

4.91. Fresenius argued that in order to solve the objective problem, the average person skilled in the art would look at improvements suggested for comparable antipholates. Fresenius refers in this respect to Chapter 12 of the same Jackman volume (exhibit 32 of Fresenius). When describing the Lometrexol and LY309887 antifolates, it mentions, among other things, '*modulating antifolate toxicities through vitamin supplementation*' and states that '*the biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B12 and B6*'. On the basis of this information, the invention claimed in conclusion 2 is not obvious for the same reasons as were assessed on the basis of the knowledge about the relationship between folate and vitamin B12 (see 4.72 and following). Also based on this information, the average person skilled in the art does not have a reasonable expectation that administration of vitamin B12 will reduce the side effects of pemetrexed without impairing the effect of pemetrexed, partly in view of the scepticism that existed about the effect of administration of vitamin B12.

4.92. In addition, Lilly rightly argued that the average person skilled in the art will see that the quotes from Jackman referred to are suggestions that are not supported by research. Jackman even explicitly mentions in the chapter referred to that the folate status of cancer patients has not been systematically evaluated. Partly in view of the scepticism that existed about the effect of the administration of vitamin B12, the average person skilled in the art would not reasonably expect to solve the objective problem by adding vitamin B12 to the combination of pemetrexed and folic acid on the basis of just such an unsubstantiated suggestion.

4.93. Moreover, before considering adding vitamin B12 to a treatment with pemetrexed, the average person skilled in the art would check whether more is known about the other antifolates described in Jackman. He will then come across the publication by Laohavinij, discussed above, which describes a clinical trial of the combination of Lometrexol and folic acid (annex 3 to Lilly's exhibit 58). As considered above, Laohavinij explicitly states in that publication that the administration of folic acid will circumvent the effect of the antifolate or even support tumour growth, and the results of her research do not remove that concern. Moreover, it is not disputed that the average person skilled in the art knew on the priority date that the development of Lometrexol had been halted. Jackman's stated pointer therefore leads the average person skilled in the art to a dead end.

conclusion inventiveness

4.94. On the basis of the above, it must be judged that Fresenius' attack on the inventive step of conclusion 2 of EP 508 was unsuccessful. This means that that conclusion must be considered valid. In that state of affairs, the validity of the other claims of EP 508 cannot be called into question, since infringement of claim 2 of EP 508 is sufficient to allow Lilly's claims, and an application by Fresenius for invalidity of the patent is not pending.

4.95. This result is in line with the decision of the Opposition Division of the European Patent Office on EP 508 (exhibit 7 of Lilly) cited by Lilly and the judgement of the Swiss court on the Swiss part of EP 508 (exhibit 48 of Lilly) (and the judgement of the American and Japanese courts on a parallel American and Japanese patent respectively). The Court is aware that the outcome does differ from the judgment of the German Bundespatentgericht on the German part of EP 508. However, on the basis of the assertions and evidence submitted by the parties to these proceedings, the Court cannot support the conclusion of the German court that the invention claimed in claim 2 was obvious to the average person skilled in the art.

claims

4.96. Assuming that Fresenius' product falls within the scope of protection of claim 2 of EP 508 and that that claim is valid, it must be concluded that Fresenius infringed the patent by marketing that product. Indeed, Fresenius has expressly acknowledged that it knows that its product is used in combination with vitamin B12 and folic acid for the treatment of cancer (claim in reply, paragraph 21(b)). In view of this, Fresenius infringed the patent directly, because Fresenius foresaw that the medicinal product manufactured by it would be deliberately used for the treatment covered by the patent (inhibiting tumour growth), and/or indirectly, because Fresenius offered and supplied the product to persons not entitled to use the invention when it knew that the product was suitable and intended for the patented indication.

4.97. In view of the above assessment of the infringement, the prohibition of infringement claimed by Lilly is admissible. That Fresenius would otherwise be guilty of wrongful acts does not follow from Lilly's claims. The prohibition of unlawful conduct will therefore be rejected.

4.98. Lilly did not explain its interest in the claimed declaratory judgment in addition to the prohibition to be granted and the order for damages to be awarded, even after Fresenius had argued that Lilly had no interest in doing so. That claim will therefore be dismissed for lack of interest.

4.99. Fresenius has rightly pointed out that an auditor cannot certify the statement of Fresenius on the basis of his professional rules. The primary claim should therefore be rejected. In the alternative, Lilly demanded that an accountant draw up a report of findings. Fresenius has not argued that that claim is also unenforceable or that Lilly has no interest in it. Therefore, the application in the alternative is granted.

4.100. With regard to the content of the statement, Fresenius rightly argued that Lilly has no interest in a renewed statement of the data that Fresenius Lilly has already provided in execution of the summary judgment (the data claimed under a, b and c). After that date, the prohibition imposed by that judgment initially applied. Although that was temporarily revoked by the court's negative judgment in this case, Fresenius argued undisputedly that she had not carried out any reserved acts in the Netherlands since the judgment in summary proceedings. It must therefore be assumed that Lilly has no interest in this statement and will only be allocated the statement of profit (the data claimed under d).

4.101. In view of the above established fact that Fresenius has not performed any reserved acts in the Netherlands since the summary judgment and the time that has elapsed since that judgment, there is no reason for the claimed *recall of* products. Nor can it be presumed that Lilly has an interest in the claimed rectification in the light of what Fresenius has submitted in that regard.

4.102. The prohibitions and orders to be allocated will be reinforced with periodic penalty payments. In order to avoid execution disputes, the penalty payments for the prohibition will be capped at € 10,000,000 and those for the other convictions at € 1,000,000.

4.103. The claimed compensation and profit remittance will also be allocated, on the understanding that the profit remittance cannot cumulate with the compensation for damage consisting of loss of profit. Therefore, in the loss statement procedure, Lilly will have to make a choice between the transfer of profits and compensation for damages consisting of lost profits, in addition to compensation for any other damages. Fresenius' argument that it did not know, and could not reasonably have known, that it was infringing must be rejected. Fresenius did not dispute the fact that Lilly had repeatedly drawn its attention to the fact that it had committed an infringement. The fact that Fresenius erred over the scope

of protection of EP 508 on the basis of - later annulled - judgments of foreign courts must be attributed to her.

4.104. As a largely unsuccessful party, Fresenius must be ordered to pay the costs of the proceedings at first instance and in principal and incidental appeal. The parties have agreed that the reasonable and proportionate costs of the proceedings at first instance and the interlocutory proceedings between the parties in two instances can be estimated together at € 400,000. Since Lilly has already claimed payment of € 150,000 in the interlocutory proceedings, it is entitled to € 250,000 for the first instance of these proceedings on the merits. As regards the appeal of these proceedings on the merits, the parties have agreed that the costs should be estimated at € 300,000 for the principal and incidental appeal jointly. The Court of Appeal sees no reason to deviate from that budget.

4.105. Finally, it is undisputed that Lilly paid Fresenius € 400,000 in execution of the order to pay the costs of the proceedings imposed by the judgment under appeal. The claim for repayment of that amount is therefore also allowable.

5 The decision

The Court of Appeal

5.1. sets aside the judgment of the District Court of The Hague of 19 July 2019 between the parties and by new judgment:

5.1.1. orders Fresenius to cease and desist any direct or indirect infringement of EP 508 in the Netherlands with immediate effect after service of this judgment, on pain of forfeiture of a penalty payment of € 100.000,- for each day or part of a day that Fresenius fails to comply with the order in whole or in part, or - at the free choice of Lilly - for each infringing product with which Fresenius fails to comply in whole or in part with the order, up to a maximum of € 10,000,000;

5.1.2. orders Fresenius to submit to Lilly's attorney at law, within 21 days after notification of this judgment, a complete, correct and verifiable statement of the profit earned by Fresenius as a result of the infringing acts in the Netherlands, specified per infringing product sold and/or delivered, supported by clearly legible orders, order confirmations, invoices and copies of other purchase and sales documents and documentation to support any deductions from the turnover and profit to be declared;

5.1.3. orders Fresenius to provide Lilly's attorney at law, within 21 days after service of this judgment, with a report containing factual findings, drawn up by an independent chartered accountant, with whom and with whose firm Fresenius has no prior relationship, with findings regarding the (estimated) amount of the profits of Fresenius obtained as a result of the infringing activities in the Netherlands, which report should contain factual findings regarding the data and documents mentioned above in 5.1.2;

5.1.4. orders Fresenius to pay an immediately due and payable penalty of € 25.000,- for each violation by Fresenius of the orders imposed under 5.1.2 and 5.1.3, or, at the free choice of Lilly, for each day that Fresenius violates these orders, with a maximum of € 1.000.000,-;

5.1.5. orders Fresenius to compensate Lilly for the damages suffered and to be suffered by Lilly as a result of the infringement of EP 508 in the Netherlands by Fresenius or - at the choice of Lilly - the profit made and to be made by Fresenius as a result of the infringement of EP 508 in the Netherlands, to be accrued to Fresenius in accordance with the law, plus statutory interest from the day of 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 € 250,000, stipulating that if these costs are not paid within two weeks after service of this judgment, Fresenius will owe legal interest on them without further summons;

5.1.7. rejects what Lilly has progressed more or differently;

5.2. orders Fresenius, in repayment of what Lilly has paid to Fresenius in compliance with said judgment, to pay an amount of € 400,000 to Lilly, increased with the statutory interest thereon as of 11 July 2019;

5.3. orders Fresenius to pay the costs of the principal and incidental appeal, up to now estimated at € 300,000 with provision that Fresenius must pay statutory interest on these legal costs from two weeks after the date of this judgment;

5.4. declares this judgment enforceable notwithstanding appeal.

This judgment was handed down by P.H. Blok, J.W. Frieling and M.W.D. van der Burg and was signed and publicly pronounced by J.E.H.M. Pinckaers, acting as docket judge, on 27 October 2020 in the presence of the Registrar.

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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 HR 5 February 2016, ECLI:NL:HR:2016:196, Bayer-Sandoz, par. 3.3.7.
3 HR 4 April 2014, ECLI:NL:HR:2014:816, Medinol-Abbott, par. 3.5.2.
4 HR 25 May 2012, ECLI:NL:HR:2012:BV3680, Aga-Occlutech, r.o. 4.2.6.
5 High Court 15 May 2014, [2014] EWHC 1511 (Pat) (*Actavis/Lilly*).
