[Notarised copy]

FEDERAL PATENT COURT

IN THE NAME OF THE PEOPLE

JUDGEMENT

Declared on 17 July 2018 Paffrath Senior Judicial Clerk as Registrar of the Court

3 Ni 23/16 (EP)
bound with 3 Ni 19/17 (EP)

(Docket number)

In the patent nullity matter

1. Hexal AG, Industriestrasse 25, 83607 Holzkirchen, legally represented by the management board S. Piret-Gérard, Dr. A. Eberhom, W. Späth, M. Weber, D. Ziebold, ebenda

Plaintiff in the proceedings 3 Ni 23/16,

Attorneys of record: LEDERER & KELLER mbB European Patent and Trade Mark Attorneys, Unsöldstrasse 2, 80538 Munich,

2. STADA Artzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, legally represented by the management board Dr. M. Wiedenfels and H. Kraft, ibid.,

Plaintiff in the proceedings 3 Ni 19/17,

Attorneys of record: Kernebeck patent attorneys LLC,
Stiftstrasse 2, 60313 Frankfurt am Main,

versus

Eli Lilly and Company, Indianapolis, Indiana 46285 (V.St.A.),

Defendant,

Attorneys of record: Hogan Lovells International LLP,
Kennedydamm 24, 40476 Düsseldorf,

regarding the European patent 1 313 508
(DE 601 27 970)

the 3rd Senate (Nullity Senate) of the Federal Patent Court has ruled on the basis of the oral hearing of 17 July 2018 by the presiding Judge Schramm and the Judge Kätker, the Judge Dipl.-Chem. Dr. Münzberg, the Judge Dipl.-Chem. Dr. Jäger and the Judge Dipl.-Chem. Dr. Wagner

has adjudged as follows:

I. The European patent 1 313 508 is revoked in its entirety effective in respect of the territory of the Federal Republic of Germany.

II. The defendant shall bear the costs of the legal dispute.

III. The judgement is provisionally enforceable against the provision of security in the amount of 120% of the amount to be enforced.

Facts of the Case

The defendant is the registered owner of the company, which was founded on June 15, 2001 pursuant to U.S. priorities US 215310 P of 30. June 2000, US

235859 P of 27. September 2000 and US 284448 P of 18 April 2001 as an international patent application PCT/US2001/014860 and the European patent applied for and granted by the European Patent Office EP 1 313 508 (Patent in suit), the grant of which was published with effect for the Federal Republic of Germany at the European Patent Office on 18 April 2007. The patent in suit is registered by the German Patent and Trade Mark Office under the number 601 27 970. The patent in suit, which is defended in its entirety and, alternatively limited with nine auxiliary requests, is entitled "Combination Containing An Antifolate And Methylmalonic Acid Lowering Agent" and comprises 14 patent claims, the ancillary patent claims 1 and 12 of which are 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-chlo-rocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin.

12. A product containing pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyrano-10-ohlorocobalamin, 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-5,8 7,8-tetrahydrofolic add, or a physiologically available salt or ester thereof, as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumor growth.

For the wording of the claims directly or indirectly related to withdrawn patent claims 1 and 12, reference is made to the patent in suit specification EPC 1 313 508.

Plaintiffs, which are both challenging the patent in suit in its entirety, are asserting respectively the grounds for nullity of lack of patentability. They base their arguments, inter alia, on the following documents:

NIK1	EP 1 313 508 B1 (Patent in suit)
NIK2	Calvert, H., Seminars in Oncology 1999, 26, No. 2, suppl. 6, pages 3 to 10
NIK3	Worzalla, J. F. et al:, Anticancer Research 1998, 18, pages 3235 to 3240
NIK8	Niyikiza, C. et al., Abstract 609P, Annals of Oncology 1998,.9, suppl. 4, pages 126 to 127
NIK9	Brattström, L., The Journal of Nutrition 1996, 126, pages 1276S to 1280S
NIK14	"Interactions™: IBIS Guide to Drug-Herb and Drug-Nutrient Interactions™, Generic Name: Methotrexate", Copyright©1998-1999 Integrative Medical Arts Group, Inc., http://www.IBISmedical.com, 13 pages
NIK15	Jackman, A. L. (Ed.), "Antifolate Drugs in Cancer Therapy", Humana Press Inc. Totowa, New Jersey, 1999, pages 183 to 201 and 261 to 280
NIK16	Niyikiza, C. et al., Proceedings of ASCO 1998, 17, Abstract *2139
NIK18	Grounds of the decision of the European Opposition Division in opposition to EP 1 313 508 (application no.: 01 948 214.0) of 27 December 2010, 17 pages
NIK19	Niyikiza, C. et al., Molecular Cancer Therapeutics 2002, 1, pages 545 to 552
NIK20	Brattström, L. et al., Metabolism 1988, 37, pages 175 to 178
NIK22	Scott, J. M., Proceedings of the Nutrition Society 1999, 58, pages 441 to 448
NIK23	Cripps, C. et al., Annals of Oncology 1999, 10, pages 1175 to 1179
NIK40	Adjei, A. A., J. Clin. Pharmacol., 1999, 48, pages 265 to 277
NIK41	Roberts, J. D. et al., Cancer Chemother. Pharmacol. 2000, 45, pages 103 to 110

NIK42 Morgan, S. L. et al.; Arthritis and Rheumatism 1990, 33, pages 9 to 18

Pursuant to the plaintiffs' submission, the subject matter of the patent in suit is not patentable.

The subject matters of patent claims 1 to 8 and 12 to 14 were anticipated by the printed publication NIK3 as harmful to novelty. NIK3 concerns a study on the effect of the additional administration of folic acid on the toxicity and efficacy of pemetrexed disodium in the intraperitoneal treatment of mice with implanted tumors, wherein folic acid was administered via the standard diet. The standard food specifically disclosed in the printed publication also contained vitamin B12 as a dietary supplement, so that vitamin B12 was applied to the mice in addition to folic acid. The study had shown that the toxic effects of pemetrexed were significantly less pronounced in those experimental animals which were given the vitamins folic acid and B12 via the standard diet. This reveals the toxicity-reducing effect of additional administration of folic acid and vitamin B12.

In addition, the subject matter of the patent in suit did not involve an inventive step either.

With reference to the NIK22, the plaintiffs state that as part of the person skilled in the art's efforts to reduce pemetrexed-related side effects while maintaining the efficacy of the active substance, the person skilled in the art will address the linkages of the folate metabolism. The methylation cycle and the DNA cycle would be linked via it. An antifolate interrupts the folate balance at certain points so that the DNA cycle breaks down and the rapidly dividing cancer cell with its increased folate requirement dies. However, the interruption of the folate balance also has harmful effects on the healthy cell. The folate metabolism must therefore be maintained to such an extent that the healthy cell can replicate further. However, the dose reduction that was initially offered here had proved unsuccessful. On the other hand, the addition of folic acid is more promising. The plaintiffs refer in

particular to the printed publication NIK15 pursuant to which the addition of folic acid permits considerably higher doses of antifolate. This is confirmed by the other printed publications HLNK3 and HLNK4. If the person skilled in the art can reduce the side effects by adding folic acid, he also has reason to add vitamin B12, since this is required for the conversion of homocysteine into methionine and of 5-methyltetrahydrofolate into tetrahydrofolate and thus for the maintenance of the methylation cycle and the DNA cycle. This is all the more true since a vitamin B12 deficiency often occurs in cancer patients with often disturbed folate metabolism. The vitamin B12 supplement is thus considered the means of choice, so that the combination in accordance with the patent in suit is anticipated.

In addition, the subject matter of the patent in suit was respectively anticipated by one of the printed publications NIK8 or NIK16 in conjunction with the expert knowledge. NIK8 and NIK16 reported two Phase II clinical trials in which a correlation was found between initially elevated homocysteine levels and pemetrexed side effects. For this purpose, the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were identified as potential indications before the start of treatment. As a result, a strong correlation of side effects with elevated homocysteine levels was found before the start of treatment.

Even if there is no indication in the printed publications of a correlation between the vitamin B12 metabolite methylmalonic acid (MMA), which was also measured, and the pemetrexed side effects, and even if NIK16 states that there was no correlation between toxicity and the other remaining predefined predicators, it cannot be concluded that there is no such correlation with regard to the vitamin B12 metabolite MMA. Rather, the person skilled in the art would have understood, pursuant to the printed publications, that the authors suspected an influence of vitamin B12 on the side effects of pemetrexed, but had not yet conclusively carried out a corresponding analysis and therefore had not yet presented the results in the short publications NIK8 and NIK16, but only in the subsequently published publication NIK19. However, this already gave the person skilled in the art reason to determine the corresponding values of the MMA themselves and to evaluate

them with regard to a possible correlation, which then led to the subject matter of the patent in suit without inventive activity, especially since it corresponded to general expert knowledge that increased homocysteine values occurred as a result of folic acid and/or vitamin B12 deficiency and that this deficiency could be compensated for by appropriate nutritional supplements.

Even the subject matters of the secondary claims, insofar as they were not already anticipated by the NIK3 citation, were not based on inventive step.

This also applied to the subject matters of the auxiliary requests, insofar as these were not inadmissible anyway.

The plaintiffs request that

> the European Patent EP 1 313 508 is revoked in its entirety effective for the territory of the Federal Republic of Germany.

The defendant requests

> the dismissal of the actions,
>
> alternatively, that the actions be dismissed with the proviso that the patent in suit receives the wording of one of the auxiliary requests 1 to 9 (in the language of the case) pursuant to the procedural document of 26 April 2018.

Patent claim 1 pursuant to auxiliary request 1 corresponds to the granted patent claim 1 with the difference that after the word "... thereof, ..." the following feature is inserted:

> „... and after the administration of the vitamin B12 or pharmaceutical derivative thereof, ..."

In patent claim 2 the term "(6R)-5-forinyl-5,6,7,8-tetrahydrofohc acid" is orthographically corrected to "(6R)-5-formyl-5,6,7,8-tetrahydrofolic acid".

The granted claims 6, 7 and 12 to 14 are deleted. The numbering and withdrawals of the remaining patent claims are adjusted.

Patent claim 1 pursuant to auxiliary request 2 corresponds to the granted patent claim 1 with the difference that after the word "... thereof, ..." the following features are inserted:

> „... and a folic binding protein binding agent, and wherein said medicament is to be administered after the administration of the vitamin B12 or pharmaceutical derivative thereof, ..."

and that the following additional feature is added:

> „... and said folic binding protein binding agent is selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid and (6R)-5formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof."

The granted claims 2, 6 and 7 as well as 12 to 14 are deleted. The numbering and withdrawals of the remaining patent claims are adjusted.

Patent claim 1 pursuant to auxiliary request 3 corresponds to the patent claim 1 pursuant to auxiliary request 2, with the difference that after the word "thereof" the following feature is inserted:

> „... and said medicament is to be administered after the folic inding protein binding agent"

Regarding auxiliary request 2, the granted patent claim 8 is additionally deleted.

Patent claim 1 pursuant to auxiliary request 4 corresponds to patent claim 1 of auxiliary request 3 with the difference that patent claim 1 states "... wherein said medicament is to be administered after ...":

> „… pretreatment with the vitamin B12 or pharmaceutical derivative thereof followed by the folic binding protein binding agent, ... ".

Regarding auxiliary request 3, the granted patent claim 9 is additionally deleted.

Patent claim 1 pursuant to auxiliary request 5 corresponds to the patent claim 1 pursuant to auxiliary request 4, with the following feature additionally inserted:

> „... and wherein the vitamin B12 or pharmaceutical derivate thereof is to be administered in an amount of 500 µg to 1500 µg."

Patent claim 1 pursuant to auxiliary request 6 corresponds to the patent claim 1 pursuant to auxiliary request 5, that in the following additionally inserted feature instead of "... in an amount of 500 µg to 1500 µg" it states:

> „... as an intramuscular injection of 500 µg to 150 µg."

In addition, the granted patent claim 10 is deleted.

Patent claim 1 pursuant to auxiliary request 7 corresponds to patent claim 1 pursuant to auxiliary request 6, with the difference that it is written after the words "... said medicament is to be administered after the folic binding protein binding agent":

> „... and wherein the administration of the vitamin B12 or pharmaceutical derivate thereof is to be repeated every 6 to 12 weeks, ...".

Patent claim 1 pursuant to auxiliary request 8 corresponds to patent claim 1 pursuant to auxiliary request 6, with the difference that instead of "„... as an intramuscular injection of 500 µg to 1500 µg." it states:

„... as an intramuscular injection of about 1000 µg."

Patent claim 1 pursuant to auxiliary request 9 corresponds to patent claim 1 pursuant to auxiliary request 8, with the difference that it is written after the words "... said medicament is to be administered after the folic binding protein binding agent":

„... and wherein the administration of the vitamin B12 or pharmaceutical derivate thereof is to be repeated every 6 to 12 weeks, ...".

The defendant contests the plaintiffs' submission on all counts. It refers to a total of 39 documents, including in particular the following:

HLNK1 Rinaldi, D. A. et al., Abstract *1559, Proceedings of ASCO 1996, 15, page 489

HLNK2 Calvert, H., "MTA: Summary and Conclusions", Seminars in Oncology, 1999, 26, suppl. 6, title page and pages 105 to 108

HLNK3 Hammond, L. et al., Abstract 866, ASCO Annual Meeting 1998, 1 page

HLNK4 Hammond, L. et al., Abstract 620P, Annals of Oncology, 1998, 9, suppl. 4, page 129

HLNK5 Laohavinij, S. et al., Invest. New Drugs, 1996, 14, pages 325 to 335

HLNK8 "Vidal® 1999 - The Dictionary", Excerpt to Vitamin B12 Aguettant® and Vitamin B12 Allergan®, 75. Edition, 1999 and also English translation, 9 pages

HLNK9 WO 96/08515 A1

HLNK12 O'Dwyer, P. J. et al., Seminars in Oncology, 1999, 26, suppl. 6, pages 99 to 104

HLNK17 Federal Register, 1996, 61, 44, pages 8797 to 8807

HLNK18 LG München I, judgement of 20 May 2016 - 21 O 22243/15, 24 pages

HLNK31 Zervos, P. H. et. al., Abstract *907, Proceedings of ASCO 1997, 16, page 256a

HLNK33 McLean, G. R. et al., Blood, 1997, 89, pages 235 to 242

HLNK36 OLG München, judgement of 18 May 2017 - 6 U 3039/16, 60 pages

Pursuant to the defendants' submission, the subject matter of the patent in suit is patentable. In particular, it was not anticipated as harmful to novelty by the printed publication NIK3, which did not reveal any combination therapy with vitamin B12. The mere mention of the diet of the experimental animals did not constitute a clear and direct disclosure of a specific administration of vitamin B12 for therapeutic purposes. Furthermore, the defendant disputes that the food supplied to the experimental animals contained any vitamin B12 at all.

The subject matter of the patent in suit did involve an inventive step. The printed publication NIK15, composed of two chapters of a textbook, could not anticipate it. At no point does it disclose a combination of any antifolate with vitamin B12 and can therefore give no suggestion to the combination therapy in accordance with the patent in suit. Chapter 8 on pemetrexed only shows that its toxicity is manageable with dose reductions, whereas Chapter 12 deals with the antifolates Lometrexol and LY309887. It only speculates on the administration of vitamin B12. In NIK8/NIK16 and HLNK31 alone, the nutritional status was actually investigated, but no correlation with the marker for vitamin B12 was found. The metabolic effects of the antifolates discussed in Chapter 12 of NIK15 also differ significantly from those of the active substance pemetrexed, so that the person skilled in the art does not draw any conclusions about pemetrexed from this chapter. The person skilled in the art therefore had no reason to base their considerations on a combined administration of pemetrexed and folic acid and to take vitamin B12 into account.

Moreover, even on the basis of a combined administration of pemetrexed and folic acid, the use of pemetrexed disodium in combination with vitamin B12, in accordance with the patent in suit, was not anticipated. Contrary to the plaintiffs' submission, the administration of vitamin B12 in addition to folic acid is neither mandatory nor customary in the relevant expert field. The problem of masking a vitamin B12 deficit by an elevated folic acid level plays a role in nutrition but not in chemotherapy. The person skilled in the art would also not have had to fear a vitamin B12 deficiency resulting from the so-called "methyl trap". As can be seen from the schematic representation of the folate balance pursuant to NIK22 , the cycle between tetrahydrofolate, 5,10-methylenetetrahydrofolate and dihydrofolate, in which folic acid flows in and in which antifolates such as pemetrexed attack key enzymes required for folate, is independent of vitamin B12. In the case of folic acid supplementation, the supply of folic acid is therefore guaranteed, so that a disturbance affecting the methylation cycle, in which vitamin B12 can play a role, does not occur in the first place.

Likewise, the subject matter of the patent in suit was also not anticipated by the printed publications NIK8 or NIK16 respectively in conjunction with the expert knowledge. These printed publications would not provide any evidence of a causal link between vitamin B12 status and the side effects of pemetrexed and thus would not stimulate the additional administration of vitamin B12 in treatment with pemetrexed. They only disclosed statistical evaluations according to which the homocysteine level was not relevant for the occurrence of pemetrexed toxicities, but the methylmalonic acid level specific only for vitamin B12 was.

In particular, the person skilled in the art had to fear that an additional administration of folic acid would impair the effectiveness of the pemetrexed treatment because of the mechanism of action of folates or folic acid and antifolates in the folate balance known to them. Therefore, the prior art indicates that the toxicities caused by Pémetrexed are manageable and tolerable with other measures. As examples, the defendant cites dose variations, combinations with other cancer medicaments or the administration of toxicity-lowering agents.

Moreover, administration of vitamin B12, even if the person skilled in the art had considered it, would have been associated with the risk of loss of efficacy of the anti-folate, whereas, conversely, vitamin B12 depletion is known to increase the effect of the anti-folate.

In addition, the printed publication NIK14, the public disclosure of which the defendant contests, anticipates a combination therapy with vitamin B12. This printed document concerns firstly, the use of methotrexate, that is to say, another antifolate, and, secondly, the treatment of rheumatoid arthritis, which differs significantly from the treatment of cancer with methotrexate in terms of the amount of active substance administered and the duration of the treatment: therefore, statements concerning vitamin B12 in NIK14 are not relevant to the treatment of cancer with methotrexate and therefore not to the treatment of cancer with pemetrexed disodium.

The defendant refers additionally to the decisions of the European Patent Office, the infringement courts and foreign courts in which the patent in suit and parallel patents were regarded as final.

According to the knowledge and the understanding of the person skilled in the art, the defendant offers expert evidence on several occasions.

Grounds for the decision

The action, based on grounds for nullity, of lack of patentability (Art. II Section 6 (1) No. 1 Int.Pat.Conventions in conjunction with Art. 138 para. (1)(a) EPU) is admissible and proves to be well-founded.

I.

1. The patent in suit concerns the use of pemetrexed disodium in combination with vitamin B12 to inhibit the growth of tumours in mammals and a product containing these components (see NIK1 patent claims 1 and 12).

In the patent in suit specification, it is explained in the introduction that antifolates belonged to the best investigated classes of antineoplastic agents. They led to the inhibition of one or more key enzymes for the biosynthesis of thymidine and purine by competing with reduced folate for the binding of these enzymes. Examples of such antifolates include 5-fluorouracil, Tomudex®, methotrexate, lometrexol and pemetrexed disodium (= Alimta®) (cf. NIK1 para. [0002]).

The limiting factor for the development of such medicaments is the considerable toxicity, which sometimes even results in a high mortality risk (see NIK1(0003)). In order to counter the toxicities and to allow a safe maximum dosage, pursuant to the information in the patent in suit specification, a supportive intervention is routinely used in some cases. For example, steroids such as dexamethasone would be used to prevent the formation of rashes caused by the antifolate (see NIK1 para. [0001]). Folic acid and retinoid compounds such as vitamin A had been used as further means of reducing toxicity. Finally, effects of vitamin B12, folate and vitamin B6 supplements in elderly persons with normal serum vitamin concentrations and homocysteine levels were found to be predictive of cytotoxic occurrences associated with the use of certain antifolates. Nevertheless, the cytotoxic activity of antifolates continues to give rise to serious concern in the development of such medicaments (cf. NIK1 para [0004]).

2. Against this background, the patent in suit has the task of improving therapeutic use of pemetrexed disodium for tumour treatment by reducing the toxic effects of the pemetrexed disodium used while maintaining improvements in the desired effects (cf. BGH, GRUR 2016, 921, para. 10 et seq. - Pemetrexed).

3. This task is solved pursuant to the ancillary patent claims with the following features:

Patent claim 1

A Use of pemetrexed disodium

B for the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals,

C wherein the medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof,

D whereby the pharmaceutical derivative of vitamin B12 is hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorcobalamin perchlorate, azidocobalamin, chlorcobalamin or cobalamin.

Patent claim 12

A Product containing pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof

B whereby the pharmaceutical derivative of vitamin B12 is hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorcobalamin perchlorate, azidocobalamin, chlorcobalamin or cobalamin

C and optionally containing a folic acid binding protein binder selected from the group consisting of folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid or (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid or a physiologically available salt or ester thereof,

D. as a combination preparation for simultaneous, separate or sequential use in inhibiting tumour growth.

4. The person skilled in the art in charge in the case at hand is a team consisting of a *pharmacologist* specialising in the mechanisms of action of antifolates and

with many years of professional experience in the research of antifolates in the treatment of cancer, and a *physician specialising in oncology* and with many years of experience in the chemotherapeutic treatment of cancer patients with anticancer agents such as antifolates (cf. BGH, GRUR 2016, 921, marg. no. 22 - Pemetrexed).

II.

The subject matter of the patent in suit, as worded in the main request, does not prove to be valid due to lack of patentability.

1. As a result, it remains to be seen to what extent there is a lack of novelty as asserted by the plaintiffs, since the use pursuant to patent claim 1 is not based on an inventive step anyway.

a) In determining whether the inventive step is to be denied, the decisive factor is whether the prior art on the priority date anticipated the subject matter of the invention to the person skilled in the art. This requires, on the one hand, that the person skilled in the art, with the knowledge and skills acquired through training and professional experience, has been able to develop the solution to the technical problem in accordance with the invention from what is existing. On the other hand, it must be added that the person skilled in the art had reason to follow the path of the invention. As a rule, this requires impulses, stimulations, hints or other occasions for the recognition of the technical problem (BGH GRUR 2009, 746 LS - Operation of a safety device, BGH GRUR 2010, 407 LS - one-piece eyelet, BGH GRUR 2012, 378, LS, marg. no. 17 - installation equipment II). When examining whether the prior art has anticipated the inventive solution to the person skilled in the art on the basis of a citation, it is not only necessary to take into account what results directly and unequivocally from this citation for the person skilled in the art, but equally what the person skilled in the art can derive from it by virtue of their expert knowledge (BGH GRUR 2013, 363 LS 2 — polymer composition).

b) Taking these principles into account, the provision of the use claimed by patent claim 1 proves to be anticipated with regard to the NIK15 in conjunction with NIK8 or NIK16 and the expert knowledge represented, for example, by NIK22.

Within the range of vision of the person skilled in the art, who is entrusted with the search for a solution of the task in accordance with the patent in suit, lies the administration of folic acid - as already the patent in suit shows in the introduction (cf. NIK1 para. [0004]) - since the information of the patent in suit can result in the treatment of toxicities which are caused by pemetrexed as inhibitor of the folate necessary key enzymes of the thymidine and purine biosynthesis pathways. For further information on folate treatment in conjunction with pemetrexed, the person skilled in the art consults the NIK15 printed publication. In Chapter 8 of this textbook excerpt, we deal with the findings known in 1999 from preclinical and initial clinical studies on pemetrexed, known there as MTA or LY231514 (cf. NIK15, p. 184, Fig. 1, lower formula). This printed publication describes the result of *in vivo*- experiments in mice have shown that an excellent antitumour dose response rate in the absence of mortality is observed by daily administration of folic acid. The experimental data even indicates that, at least in animal experiments, folic acid supplementation not only modulates the toxicity of pemetrexed, but even slightly increases the antitumour response rate (cf. NIK15 p. 190/191 pp. paras., in particular third and last sentence). The person skilled in the art thus takes from this printed publication the positive influence of folic acid supplementation in an antitumour treatment with the antifolate pemetrexed.

The pharmacologist in the responsible team of persons skilled in the art takes a closer look at the biochemical reactions in which folic acid is involved, knowing this positive influence. They know from the folate balance that tetrahydrofolate is formed from folic acid, which in turn plays a central role in C1 metabolism as well as in the synthesis of purine bases and thus in cell replication (cf. NIK22 p. 442 Fig. 1). A closer look at the folate balance shown in Fig. 1 of NIK22 reveals to the person skilled in the art that the tetrahydrofolate and its precursor 5-methyltetrahydrofolate connect the lower cycle, referred to in this printed

publication as the "DNA cycle", with the upper cycle, referred to as the "methylation cycle", whereby the conversion of 5-methyltetrahydrofolate into tetrahydrofolate is regulated by the vitamin B12-dependent enzyme methionine synthase (cf. NIK22 p. 444). 444 purl. column paras. 3 p. 6 to 9).

Due to this connection between the two cycles, the person skilled in the art knows from the folate balance that when pemetrex is administered by blocking the three key enzymes thymidylate synthase (= TS), dihydrofolate reductase (= DHFR) and glycinamide ribonucleotide formyl transferase (= GARFT) in the "DNA cycle" not only this cycle but also the "methylation cycle" is blocked (cf. NIK1 para. [0002] last sentence, NIK15 p. 184 para. 1 second last sentence). This biochemical relationship is confirmed by the correlation between the homocysteine level before the start of treatment and the observed toxicities during pemetrexed treatment described in NIK8 and NIK16 (cf. NIK8 and NIK16, respectively, entire Abstract). Homocysteine is a substrate in the "methylation cycle", which is also indirectly influenced by the attack of the antifolate on the "DNA cycle" and thus also the homocysteine level.

Furthermore, they know from the folate constitution that the enzyme methionine synthase and thus also the homocysteine level is regulated by both folic acid and vitamin B12. In other words, the administration of one or both of these vitamins increases the activity of methionine synthase, which leads to a reduction in homocysteine levels. Knowing the results of NIK8 and NIK16, which show that there is a strong correlation between homocysteine levels and the side effects of pemetrexed treatment, and being aware of the physiological relationships of the folate balance, the person skilled in the art is therefore motivated to turn to vitamin B12 as an important regulator of the folate balance in addition to folic acid, which has already been tested positive, in order to be able to counteract the toxic side effects of pemetrexed treatment. Thus the use claimed in patent claim 1 with all features results from the doctrine of NIK15 and NIK8 or NIK16 in conjunction with the expert knowledge pursuant to NIK22 without inventive activity.

c) The defendant's argument that folic acid administration activates only the 'DNA cycle' without the involvement of methionine synthase cannot be accepted.

As indicative that the patent in suit is known expert knowledge, Pemetrexed inhibits the three key enzymes of the thymidine and purine biosynthetic pathways TS, DHFR and GARFT. This entirely prevents the supply of the tetrahydrofolate required for DNA synthesis, not only in tumour cells but also in healthy cells. This results in the serious side effects observed. Folic acid supplementation can reactivate tetrahydrofolate production in the cell however to such an extent that the side effects can be alleviated by targeted promotion of DNA biosynthesis. The cycle of tetrahydrofolate, 5,10-methyltetrahydrofolate and dihydrofolate, referred to by the defendant as 'the supply route', is initiated, thereby removing the blocking of the 'DNA cycle' responsible for the side effects of pemetrexed treatment. This activation of the "supply pathway" also leads to the increased formation of 5.10-methylenetetrahydrofolate. In the folate balance, this not only reacts further to dihydrofolate, but is also converted to 5-methyltetrahydrofolate in a second, alternative way by means of 5,10-methylenetetrahydrofolate reductase, which - as already discussed - is then converted to tetrahydrofolate by means of vitamin B12-regulated methionine synthase (cf. NIK22 Fig. 1). This second reaction pathway is neither inhibited nor switched off by the administration of pemetrexed, since pemetrexed does not inhibit the two regulating enzymes 5,10-methylenetetrahydrofolateductase and methionine synthase. In addition, 5-methyltetrahydrofolate can be supplied from the plasma (cf. NIK22 Fig. 1). Therefore, there is no reason for the person skilled in the art to assume that the second reaction pathway via 5-methyltetrahydrofolate no longer plays a role after folic acid administration. All the more, they will even consciously envisage this path, since it is independent of the inhibitory effect of pemetrexed on the key enzymes of the "DNA cycle".

The observation that the toxicity of pemetrexed treatment correlates with the homocysteine level in the blood serum (cf. NIK8, NIK16, HLNK31, each entire Abstract, HLNK2 p. 106 right column line 17 to 12 from end) also argues against

the thesis that the "DNA cycle" in folic acid administration runs independently of the "methylation cycle". This is explained by the fact that hornocysteine is part of the "methylation cycle", which in turn is linked to the "DNA cycle" via methionine synthase (cf. NIK22 p. 442 Fig. 1). However, due to the correlation of the homocysteine level with the serious side effects of pemetrexed treatment, the person skilled in the art recognises that the folate balance in its entirety is influenced by pemetrexed treatment pursuant to Fig. 1 of NIK22 and therefore cannot control the two cycles independently of each other.

The person skilled in the art's knowledge of the so-called "methyl trap" also encourages them not to ignore the second reaction pathway via 5-methyltetrahydrofolate. The person skilled in the art understands the methyl trap as a disturbance of DNA biosynthesis in which the folate cofactors in the form of 5-methyltetrahydrofolate are "trapped", i.e. no longer metabolised. As a result, the cell suffers from a so-called pseudofolate deficiency, although there is enough folate or folic acid available (cf. NIK22 p. 445 r.). 445 right column para. 2 p. 14 to 32). The person skilled in the art is familiar with the intramuscular administration of vitamin B12 as a way out of the methyl trap (cf. NIK22 p. 445 right column para. 2 p. 35 to 39), so that also this expert knowledge motivates the person skilled in the art to consider vitamin B12 for the solution of the task pursuant to the litigation patent. The person skilled in the art also does not refrain from the second known way out of the methyl trap, according to which high doses of folic acid are added, which also drives tetrahydrofolate production (cf. NIK22 S. 445 right column para. 2 p. 39 to 45 in conjunction with p. 442 Fig. 1). If the person skilled in the art considers several alternatives to solve a problem - in this case either folic acid or vitamin B12 - it may be anticipated that different paths are taken (see BGH, GRUR 2015, 356, marg. no. 31— Repaglinid).

The defendant sees further confirmation of its assumption that the administration of folic acid to reduce the side effects of pemetrexed treatment does not give rise to the administration of vitamin B12, in that despite the masking problem, i.e. the masking of a vitamin B12 deficiency, the US FDA does not recommend an

additional vitamin B12 supplementation in foods supplemented with folic acid, even for patients with pernicious anaemia (see HLNK17 p. 8801 right column para. 2). This argument cannot be accepted either. When the person skilled in the art deals with the biochemical mechanisms of action of pemetrexed and folic acid, they will inevitably encounter the folate balance in accordance with Fig. 1 of the NIK22 and - as shown in II.1.b - include vitamin B12 in their considerations on the basis of the biochemical interrelationships shown therein.

d) Contrary to what was assumed by the defendant, the prior art also shows the tendency that a combined administration of pemetrexed and folic acid is promising for efficacy in humans, which is why the person skilled in the art based their considerations on the combined administration of pemetrexed and folic acid and therefore also had reason to consider vitamin B12 in order to solve the task in accordance with the patent in suit. The printed publications HLNK3 and HLNK4 consulted for this matter, which both report the same phase 1 study on the joint administration of pemetrexed and folic acid, show that the administration of folic acid dosage increases to at least 800 mg/m^2 Pemetrexed is possible. Only 2 out of 33 patients in the study with HLNK4 showed serious side effects. The authors therefore conclude the reports with the encouraging observation that folic acid supplementation seems to allow an increase in the dose of pemetrexed due to its positive influence on the side effects (cf. HLNK3 and HLNK4 respectively entire Abstract). This means that the person skilled in the art does not take any evidence from these printed publications that would argue against a joint administration of folic acid and pemetrexed in the treatment of tumours. Rather, the conclusion in both reports motivates them to continue to deal with folic acid for the reduction of side effects in pemetrexed treatment, which the expert community has also seen in this way in the subsequent period (cf. NIK40 p. 270 left column final entire sentence with ref. [53] corresponding to HLNK3).

The fact that there were no published Phase II studies on folic acid supplementation during pemetrexed treatment at the time of the priority period does not discredit this either. The printed publication HLNK12 cited in this regard

only gives an overview of phase II studies in 1999 in which the efficacy of pemetrexed on different tumour types is investigated. However, this does not prove that folate supplementation during pemetrexed treatment has not already been investigated in further Phase II studies. The results of the phase II studies pursuant to NIK8 and NIK16 as well as HLNK31 speak for the fact that the person skilled in the art had already had folic acid administration in mind at the time of priority. There, a direct connection between the serious side effects of pemetrexed treatment and the level of homocysteine at the start of treatment is reported (cf. NIK8, NIK16 and HLNK31, respectively entire abstract). As already explained, the person skilled in the art knows from this that it is increased by a deficiency of folic acid and possibly vitamin B12 (cf. e.g. B. NIK2 p. 8/9 pp. page and p. 9 first entire sentence). With the results of the studies pursuant to these printed publications and the expert knowledge documented, for example, in NIK2, the person skilled in the art therefore not only receives an occasion to include from the joint administration of pemetrexed and folic acid despite the lack of phase II studies in their considerations, but also the stimulus to consider vitamin B12 in addition to folic acid.

The defendant's submission that the results of clinical phase II studies are necessary for a reasonable expectation of success discredits this. Clinical research is always based on *in* vitro experiments, which is proven by the cited prior art. For example, in the field of antitumour therapy relevant to the patent in suit, on the priority date there are already a large number of *in vitro*-tests as well as suitable animal models as they are also used for pemetrexed in the above-mentioned prior art (cf. e.g. B. NIK3 p. 3235 and 3236 "Materials and Methods", cf. e.g. B. NIK15 p. 185 et seqq. Chap."2. Preclinical Pharmacology Studies of MTA"). The positive results of the *in vitro*-studies and investigations on the animal models, the person skilled in the art receives, as is usual with classical medicaments, a reasonable expectation of success by including the combined use of pemetrexed and vitamin B12 based on the combined administration of pemetrexed and folic acid in their considerations.

Experience with other antifolates also suggests that the joint administration of pemetrexed and folic acid should be used as a basis for solving the problem in accordance with the patent in suit. Thus, for the longest known antifolate methotrexate, a joint administration with folic acid to mitigate the side effects was already described in 1990 (cf. NIK42 Abstract sentence 2). In this context it is not relevant that in NIK42 the therapeutic use of methotrexate as a medicament against rheumatoid arthritis and not as an antitumour agent has been investigated. This is because methotrexate also acts as an antifolate in this treatment with low medicament doses over a long administration period, with the result that it interrupts the DNA biosynthesis cycle and leads to the known side effects.

Furthermore, a daily administration of folic acid for the antifolate Lometrexol during a weekly treatment with the active substance is described as suitable, so that a phase II study is considered feasible with this dose regime (see NIK41 p. 103 title and abstract). Likewise, Chapter 12 of the NIK15 reference book on Lometrexol explicitly describes folic acid supplementation to reduce toxic side effects (cf. NIK15 p. 270 section 9 para. 1 last sentence). This chapter also refers to the biochemical cycles of the folate balance and that an adequate supply of vitamin B12 is also necessary in this context (cf. NIK15 p. 270 sec. 9 para. 2 sentences 1 and 2). This is another motivating finding to consider vitamin B12 in the solution of the task in accordance with the patent in suit, based on the combined use of pemetrexed with folic acid pursuant to Chapter 8 of NIK15.

e) Nor in the case of a supposed tumour-promoting effect of vitamin B12 is the person skilled in the art prevented from using vitamin B12 to solve the task of the patent in suit. The HLNK8 used to support this argument merely reveals a general statement regarding the contraindication of the administration of vitamin B12 preparations in malignant tumours, which, however, is not related to tumour treatment with antifolates and in particular with pemetrexed (cf. HLNK8 li. column „Vitamin B_{12} Aguettant®" para. "Contraindications"; right column „Vitamin B_{12} Allergan®" para. "Contraindications"). The additionally cited printed publications HLNK9 and HLNK33 deal with the blockade of DNA synthesis by vitamin B12

deprivation and thus with setting another task (cf. HLNK9 p. 2 line 13 to 23 and p. 4 line 13 to 15; cf. HLNK33 p. 241 right column para. 2 with Cbl = Cobalamin). They are therefore not suitable to create a prejudice against the use of vitamin B12 to treat the serious side effects of pemetrexed treatment.

f) Finally, the defendant's objection that there were a number of other ways of counteracting the serious side effects of pemetrexed treatment does not lead to any other view. On the one hand, depending on the circumstances of the field of technology concerned, there may be various possibilities for the person skilled in the art to proceed further, and accordingly it is recognised in the case law of the Federal Supreme Court that taking different paths may be anticipated (see Federal Supreme Court, GRUB 2015, 356, para. 31 - Repaglinid). In the present case, the person skilled in the art may also have considered the alternative measures put forward by the defendant, such as dose variation, combined administration with other anti-tumour agents or the administration of side effects reducing medicaments. However, this does not preclude the anticipated course of a combined administration of pemetrexed with the influencing factors folic acid and vitamin B12 which have an effect on the folate balance. On the other hand, the prior art for pemetrexed shows the positive effect of a combined use of pemetrexed and folic acid (cf. NIK15 p. 190/191 pp. para.; NIK23 p. 1179 left column para. 2; NIK40 S. 270 left column final entire sentence; HLNK3 and HLNK4 respectively last sentence). This provides the person skilled in the art with an explicit encouragement to continue working on this particular approach.

g) The above statements on inventive step also do not contradict the decisions of the Regional Court Munich I HLNK18 and the Higher Regional Court Munich HLNK36 regarding interim injunction proceedings concerning the patent in suit because the infringement courts base their postulated legal validity of the patent in suit in particular on the justifiability of the decision of the Opposition Division of the European Patent Office NIK18 (see HLNK18, p. 18/19, p. 18/19, pp. para.; HLNK36 p. 55 para. b)). However, the NIK18 decision did not discuss inventive step based on NIK15 in combination with NIK8 or NIK16 in combination with the

expert knowledge documented in NIK22. Taking account of decisions HLNK18 and HLNK36 in conjunction with NIK18 therefore does not lead to a different assessment of the facts.

2. Since the defendant stated at the hearing that their application was to be regarded as concluded pursuant to the main request, it is not necessary to determine whether in the ancillary and subordinate patent claims 2 to 14 a valid remnant can be recognised (see BGH GRUR 2007, 862 - Information Transmission Procedure II; BGH GRUR 1997, 120 - Electric Storage Heater; BPatG GRUR 2009, 46 - Ion Exchange Procedure).

III.

The inferential wording pursuant to the auxiliary requests 1 to 9, which was alternatively defended by the defendant also proves to be invalid on account of lack of inventive step.

1. Patent claim 1 pursuant to auxiliary request 1 differs from patent claim 1 pursuant to main request in that pemetrexed disodium is now administered pursuant to how vitamin B12 or vitamin B12 derivative is administered.

However, this additional feature cannot establish the basis of the use of an inventive step as the subject matter of the dispute. The person skilled in the art knew from the studies pursuant to NIK8, NIK16 and HLNK31 that there is a strong correlation between homocysteine level and the serious side effects of pemetrexed treatment (cf. loc. cit in respectively entire Abstract; cf. also HLNK2 p. 106 right column line 17 to 12 from end). With this knowledge, there was no need for inventive activity to lower the homocysteine level before the start of treatment by administering vitamins such as vitamin B12 (see NIK9 and others p. 1276S Abstract last sentence). Rather, the person skilled in the art will consider this measure within the framework of the usual optimisation in medicament development. It can therefore be attributed to their routine work.

2. For the same reason, the additional features in the respective patent claim 1 of auxiliary requests 2 and 3 cannot establish the basis of an inventive step. When used under patent claim 1 pursuant to auxiliary request 2, it is claimed the additional administration of a folic acid binding protein binding agent that, inter alia, is selected from folic acid, is opposite to the use under patent claim 1 of auxiliary request 1. In patent claim 1 of auxiliary request 3, the order of administration has also been determined in such a way that pemetrexed disodium is also applied after administration of the folic acid binding protein binding agent. These features also result in an anticipated way from the NIK8, NIK16 and HLNK31 studies and the expert knowledge of the person skilled in the art in the treatment of elevated homocysteine levels.

3. In patent claim 1 under auxiliary request 4, the order of administration is specified in such a way that vitamin B12 is administered first, followed by the folic acid binding protein binding agent and then pemetrexed disodium. The determination of the order of administration is a customary measure to be attributed to the task area of the person skilled in the art, especially since the patent in suit specification in suit does not attach any particular importance to the order of administration (cf. NIK1 Patent Claims 6, 12, p. 3, para. [0015], p. 4, para. [0021], p. 6, para. [0037]). Such a claim is therefore also not suitable for remedying the lack of inventive step.

4. The subject matter of patent claim 1 of auxiliary request 5 supplements patent claim 1 pursuant to auxiliary request 4 in the feature that vitamin B12 or the vitamin B12 derivative is to be administered in an amount of 500 µg to 1500 µg. Patent claim 1 of auxiliary request 6 also claims the intramuscular application of vitamin B12 or the vitamin B12 derivative. Both features are well known and customary for the administration of vitamin B12 compounds also in conjunction with the treatment of homocysteine levels (see NIK20 p. 175 summary and p. 175/176 pp. sentence), so that even with these features the claimed use is not patentable due to lack of inventive step.

5. In the respective patent claim 1 of auxiliary requests 7 and 8, the use pursuant to patent claim 1 of auxiliary request 6 is further substantiated by the feature of repeated administration of vitamin B12 (derivative) at intervals of 6 to 12 weeks (= auxiliary feature 7) or by the restriction of the administration quantity of vitamin B12 or vitamin B12 derivative to 1000 µg (= auxiliary request 8). Also this additional feature cannot establish the basis of the use of an inventive step as the subject matter of the dispute. This is because the administration of 1000 µg of the vitamin B12 derivative hydroxycobalamin is explicitly disclosed in NIK20 p. 176 left column p. 2, right column para. 2 p. 6). The repeated administration of the vitamin B12 or vitamin B12 derivative is a measure which the person skilled in the art considers and examines within the framework of the usual dose adjustment. It can therefore be attributed to their routine work. The subject matter of these patent claims was therefore anticipated for the same reasons as those of the respective patent claims 1 of the preceding auxiliary requests.

6. In patent claim 1 of auxiliary request 9, both additional features from the respective patent claim 1 of auxiliary requests 7 and 8 have been included in patent claim 1 pursuant to auxiliary request 6. Thus, no other argumentation applies to this patent claim than to the respective patent claim 1 after auxiliary request 7 and 8, which is why the subject matter of patent claim 1 pursuant to auxiliary request 9 was also anticipated and therefore not patentable.

A valid remainder is also not recognisable for the Senate in the subject matter of the subordinate patent claims 2 to 5 according to auxiliary request 9. The defendant has not argued that they are entitled to independently patentable content. Such is also not apparent, especially since the claimed distinguishing features folic acid, vitamin B12, hydroxocobalamin and oral administration of folic acid in tablet form are customary in the field and known from the discussed prior art (cf. NIK15 p. 190/191 pp. para.; HLNK3 and HLNK4 respectively entire Abstract; NIK22 p. 444 left column para. 2; NIK20 p. 175/176 pp. para.; HLNK5 p. 326 para. 2 sentence 1).

IV.

In accordance with the defendant's request, the Senate had no reason to seek an expert opinion on questions relating to various aspects of knowledge and understanding of a person skilled in the art, in particular on the biochemical mechanisms of action of the folate balance and on the effects of the use of antifolates, folic acid and vitamin B12 and combinations of these active substances on folate metabolism. The purpose of expert evidence is to provide the Court with expert knowledge for assessing facts or to establish facts that are germane to the decision insofar as special expertise is required for this. In proceedings before the Federal Patent Court, such evidence is not necessary as a rule, since the Nullity Divisions and the Technical Chambers of Appeal are composed of expert judges (cf. BGH GRUR 2014, 1235 guiding principle 1 and marginal note no. 8 – communication router; Schulte, PatA, 10th edition, Section 81 marginal note 157; Busse, PatA, B. ed., Section 87 marginal note 23, Section 88 marginal note 11). In particular, expert proof is not required if the court itself can acquire the necessary expert knowledge, for example by studying the specialist literature (cf. Thomas/Putzo, C.C.P, 37th ed., preliminary remark § 402 marginal note 3). According to these principles, no evidence was to be taken from experts in the case at hand, as the Division, due to its technical knowledge, was in a position to appraise, on the basis of the technical literature, in particular the extensive literature provided by the parties including several private expert opinions, the expert knowledge reflected therein for the purposes of the examination of the facts, and thus to fully recognise and appreciate the facts.

V.

The decision on costs is based on Section 84 para. 2 PatG in conjunction with Section 91 para. 1 C.C.P.

The decision on provisional enforceability follows from Section 99 para. 1 PatG in conjunction with Section 709 sentence 1 and sentence 2 C.C.P.

VI.

This judgement may be appealed.

The appellate pleading must be signed by an attorney or patent attorney admitted in the Federal Republic of Germany and filed within one month with the Federal Court of Justice, Herrenstrasse 45a, 76133 Karlsruhe. The period of appeal begins with the notification of the judgement drawn up in its entire form, but at the latest with the expiry of five months after the pronouncement.

The appellate pleading must state the designation of the judgement against which the appeal is directed, as well as the declaration that this judgement is being appealed.

Schramm Kätker Dr. Münzberg Dr. Jäger Dr. Wagner

Pr

[Seal]

[FEDERAL PATENT COURT 40]

Notarised:

[signature]

Paffrath, Senior Judicial Clerk as Registrar of the Court