Bundesgericht

4A_570/2019

Judgment from May 1, 2020
1st Civil Law Department

Member judges

Federal Judge Kiss, President,
Federal judges Niquille, May Canellas,
Court Clerk Leemann.

Participant in the proceedings

Sandoz Pharmaceuticals AG,
Suurstoffi 14, 6343 Rotkreuz,
represented by attorney-at-law Dr. Markus Wang and
attorney-at-law Julia Jung,
Brandschenkestrasse 90, 8002 Zurich,
Appellant,

against

Eli Lilly and Company,
Lilly Corporate Center, Indianapolis - Indiana 46285,
United States,
represented by attorneys-at-law Dr. Christian Hilti and
Dr. Demian Stauber,
Bellerivestrasse 203, PO Box, 8034 Zurich,
Respondent.

Subject matter

Patent nullity,

Appeal against the judgment of the Federal Patent Court
from October 15, 2019 (02018_003).

Facts:

A.

A.a Sandoz Pharmaceuticals AG (Plaintiff, Appellant) is a public limited company based in Rotkreuz.

Eli Lilly and Company (Defendant, Respondent) is an American company based in Indianapolis, United States.

A.b The Defendant is the owner of European patent EP 1 313 508 B1. The patent was filed on June 15, 2001, claiming three U.S. priorities dated June 30, 2000, September 27, 2000 and April 18, 2001. The patent was granted on April 18, 2007. The Swiss part of the patent is under discussion.

The patent in suit is directed towards a composition containing an antifolate and a methylmalonic acid-lowering agent. The granted patent in suit has the following independent claims 1 and 12 as well as claims 2-11 dependent on claim 1 and claims 13 and 14 dependent on claim 12:

1. Use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin B12 being hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin or cobalamin.

12. A product containing pemetrexed disodium, vitamin B 12 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.

Proceedings concerning the nullity of the respective part of the patent in suit were held in various countries (Germany, the Netherlands, USA, Japan, opposition proceedings before the European Patent Office).

A.c The patent in suit concerns the field of cancer treatment. Antifolates have already previously been used for cancer therapy. Antifo-

lates are analogues of folic acid, which intervene in DNA synthesis by inhibiting the corresponding enzymes and thereby prevent cell division and thus cell growth of the cancer cells. However, due to these cytotoxic effects, antifolates have serious disadvantages.

According to the patent in suit, it was surprisingly and unexpectedly discovered “that certain toxic effects, such as mortality and non-hematological 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 adversely affecting therapeutic efficacy."

B.
On February 1, 2018, Plaintiff brought an action before the Federal Patent Court with the prayer of relief that the Swiss part of EP 1 313 508 be declared null and void.

The Defendant requested that the action be dismissed on May 3, 2018.

In the reply dated September 24, 2018, Plaintiff maintained its prayers for relief.

On October 30, 2018, Plaintiff made a submission of new evidence.

With the rejoinder dated November 14, 2018, Defendant made various auxiliary requests.

On December 12, 2018 Defendant submitted a statement on Plaintiff's submission of new evidence.

On December 14, 2018, Plaintiff submitted a statement on the rejoinder with the additional prayer of relief that Defendant's auxiliary requests should also be dismissed.

On January 24, 2019 Defendant made a submission of new evidence, on which Plaintiff commented on February 8, 2019.

On March 12, 2019, the technical judge provided its expert judge opinion, which the parties commented on with submissions dated April 12, 2019 and May 7, 2019, respectively.

The main hearing took place on June 17, 2019.

By judgment of October 15, 2019, the Federal Patent Court dismissed the suit.

C.
With an appeal in civil matters, Plaintiff requests of the Federal Supreme Court that the judgment of the Federal Patent Court of October 15, 2019 be set aside and that the Swiss part of EP 1 313 508 should be declared null and void. Alternatively, the contested judgment was to be set aside and the case was to be referred back to the Federal Patent Court for reassessment.

Respondent requests that the appeal be dismissed, to the extent it can be dealt with. Alternatively, it was to be referred back to the lower court for reassessment. The lower court has refrained from a consultation.

Appellant has submitted a reply to the Federal Supreme Court, and Respondent has submitted a rejoinder.

Considerations:

1.
The Federal Supreme Court examines ex officio and with free cognition whether an appeal is admissible (Art. 29 Para. 1 BGG [Swiss Federal Supreme Court Act]; BGE 141 III 395 E. 2.1).

1.1 The appeal concerns a civil matter (Art. 72 BGG), it is directed against a decision of the Federal Patent Court (Art. 75 Para. 1 BGG), Appellant has been unsuccessful with its requests (Art. 76 Para. 1 BGG), a value in dispute is not necessary (Art. 74 Para. 2 lit. e BGG) and the appeal period has been met (Art. 100 Para. 1 BGG).

Subject to sufficient justification the appeal is to be dealt with (Art. 42 Para. 2 and Art. 106 Para. 2 BGG).

1.2 The Federal Supreme Court applies the law ex officio (Art. 106 Para. 1 BGG). It is therefore neither bound by the arguments asserted in the appeal nor by the considerations of the lower court; it can approve an appeal for a reason other than the called one, or reject an appeal with a reason that deviates from the reasoning of the lower court. With a view to the duty of the appealing party to justify

(Art. 42 Para. 1 and 2 BGG), it generally only deals with the asserted objections, unless the legal deficiencies are downright obvious; in any case, it need not consider to investigate all legal questions that arise like a lower court, if these are no longer brought forward before the Federal Supreme Court (BGE 140 III 115 E. 2 p. 116; 137 III 580 E. 1.3; 135 III 397 E. 1.4). A qualified duty to make a specific objection applies with regard to the violation of fundamental rights and of cantonal and intercantonal law. The Federal Supreme Court examines such an objection only to the extent that it has been precisely put forward and substantiated in the appeal (Art. 106 Para. 2 BGG). If, for example, the appealing party asserts a violation of the prohibition of arbitrary conduct (Art. 9 BV [Swiss Federal Constitution]), it is not sufficient if it simply asserts that the contested decision is arbitrary; rather, it has to show in detail to what extent the contested decision is obviously untenable (BGE 141 III 564 E. 4.1; 140 III 16 E. 2.1 p. 18 f., 167 E. 2.1; each with references). If the contested decision is based on several independent reasonings, the appeal must deal with each one, otherwise it will not be addressed (BGE 142 III 364 E. 2.4 p. 368 with references; see also BGE 143 IV 40 E. 3.4 p. 44).

With regard to Art. 42 Para. 2 and Art. 106 Para. 2 BGG, it is imperative that the appeal addresses the reasoning of the contested decision and shows in detail what constitutes an infringement. In the notice of appeal, the appealing party should not simply reaffirm the legal positions it had taken in the lower court proceedings, but rather direct its criticism to the considerations of the lower court that were considered to be an error in law (BGE 140 III 86 E. 2 pp. 89, 115 E. 2 p. 116). The justification must also be given in the notice of appeal itself and the mere reference to statements in other legal submissions or to the files is not sufficient (BGE 143 11 283 E. 1.2.3; 140 III 115 E. 2 p. 116).

1.3 The Federal Supreme Court bases its judgment on the facts that the lower court has determined (Art. 105 Para. 1 BGG). This includes both the findings about the facts at issue and those about the course of the lower court proceedings, i.e. the findings about the facts of the process (BGE 140 III 16 E. 1.3.1 with references). It can only correct or supplement the factual finding of the lower court if it is obviously incorrect or based on an infringement of law within the meaning of Art. 95 BGG (Art. 105 Para. 2 BGG). "Obviously incorrect" means "arbitrary" (BGE 140 III 115 E. 2

p. 117; 135 III 397 E. 1.5). Furthermore, the rectification of the defect must be decisive for the outcome of the proceeding (Art. 97 Para. 1 BGG).

The strict principle of the duty to make a specific objection according to Art. 106 Para. 2 BGG (BGE 140 III 264 E. 2.3 p. 266 with references) also applies to criticism of the established facts. The party wishing to contest the factual finding of the lower court must show in a clear and substantiated manner to what extent these requirements should be met (BGE 140 III 16 E. 1.3.1 p. 18 with references). If it wants to add to the facts, it must in addition show with precise references to the file that it has already brought forward corresponding legally relevant facts and suitable evidence before the lower courts in a process compliant manner (BGE 140 III 86 E. 2 p. 90). If the criticism does not meet these requirements, submissions with regard to a fact that deviates from the contested decision cannot be taken into account (BGE 140 III 16 E. 1.3.1 p. 18).

2.
Appellant accuses the lower court of wrongly affirming inventive step and thus of violating Article 1 Para. 2 of the Federal Act dated June 25, 1954 on patents for invention (Patent Act, PatG; SR 232.14) and Article 56 of the European Patent Convention of October 5, 1973, revised in Munich on November 29, 2000 (EPC 2000; SR 0.232.142.2), respectively.

2.1 The lower court defined the skilled person in the art as a team consisting of a chemist, a pharmacist and an oncologist, who have experience in the field of cancer treatment and the mechanisms of action of antifolates. It did not accept Appellant's objection that all patent claims were null and void due to lack of inventive step, this in particular with regard to the publication "Antifolate Drugs in Cancer Therapy" (hereinafter "Jackman") published by Prof. Jackman. Jackman is a monograph on antifolates in cancer therapy. Chapter 8 deals with studies on the multi-target antifolate (MTA) LY231514 (pemetrexed), while Chapter 12 deals with studies on the glycinamide ribonucleotide formyl transferase (GARFT)-inhibitors lometrexol and LY309887. Chapter 8 contains in section 2.6 on page 191 the following passage:

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

It can indeed be concluded from this passage that it is recommended here that folic acid be administered in combination with pemetrexed.

Immediately afterwards Fig. 4 can be found on page 192:

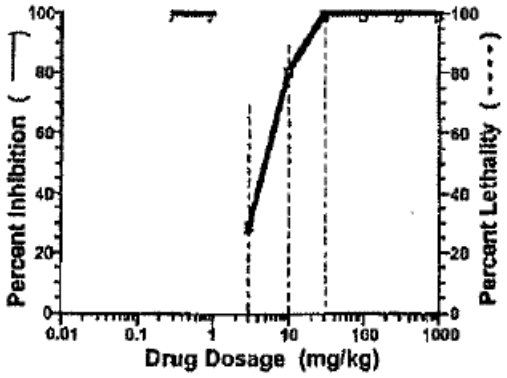

Fig. 4. Antitumor activity of MTA against L5178Y/TK⁻/HX⁻ lymphoma for mice on low folate diet (LFD) with no folate supplementation (J) and for mice on low folate diet that received 15 mg/kg/d daily folate supplementation (B); vertical dashed lines represent percent lethality in mice on low folate diet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

It is shown here that full inhibition (antitumor effect) is achieved already at a lower dose (data above left) of pemetrexed without folic acid and that upon administration of folic acid this full inhibition is only achieved with a drastically increased pemetrexed dose, at which high lethality can already be observed in case of no folic acid administration. In other words, Fig. 4 does not show an increase in the antitumor effect by folic acid, as is mentioned in the first passage ("slightly enhances the antitumor response"), but on the contrary, a reduction.

How the person skilled in the art would deal with this situation of contradicting recommendations and which one he would have followed is difficult to assess. However, he would certainly not have decided for a supporting administration of folic acid without a doubt. Even if he chose folic acid, the lower court continued, he would have been cautious and would have continued to be concerned. It is also clear that, on the other hand, the person skilled in the art would find confirmation in the two documents,

which concern phase I studies (act. 7_21, act. 7_22), that adding folic acid would require higher doses of pemetrexed, but would also learn from these that the folic acid addition would reduce the toxicity of pemetrexed.

On the basis of Fig. 4, Respondent's argument was conclusive that the person skilled in the art had no motivation to give folic acid to the patient and thereby would be forced to massively increase the dose of pemetrexed to achieve 100% inhibition, if the 100% inhibition had been achieved already at a significantly lower dose but without folic acid. This view is in line with the decision of the Court of The Hague.

It remains however undisputed that Chapter 8 contains no reference to vitamin B12 or a pharmaceutical derivative thereof. Regardless of whether the person skilled in the art would administer folic acid with pemetrexed for a treatment of cancer or not, it remains to be determined whether he would have given vitamin B12 (namely with or without folic acid) to solve the problem underlying the patent. The problem underlying the patent in suit was to reduce the toxic effects of pemetrexed without having a negative effect on the therapeutic efficiency of the antifolate. The patent in suit solves this problem by using vitamin B12 or a pharmaceutical derivative thereof, alone or in combination with folic acid.

As stated, Chapter 8 contains no reference to vitamin B12 or a pharmaceutical derivative thereof. Chapter 12 of Jackman, on the other hand, contains a reference to vitamin B12 on p. 270:

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

The biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B_{12} and B_6. Thus, the status of all three vitamins in patients may significantly influence the severity of toxicity observed during chemotherapy. R. Allen and his col-

It should however be emphasized that this passage from Chapter 12 relates to other antifolates, which, in contrast to pemetrexed, are not multi-target antifolates, and that the passage should rather be interpreted as an unproven recommendation due to the wording ("may").

Claims 1-11 of the patent in suit were directed to "mammals," which includes mice. Thus, the state of the art, which affects mice and not humans, should not be regarded as not relevant per se, but rather that the person skilled in the art would take it into account despite the differences and examine more closely the relevance in a further step. The fact that Chapters 8 and 12 are in the same monograph does not allow drawing the conclusion that the person skilled in the art would have necessarily combined their disclosures. The chapters are written by different authors and are therefore independent works. Although they both dealt with antifolates, lometrexol and LY309887 are GARFT inhibitors, while pemetrexed, in addition to GARFT, also inhibits thymidylate synthase (TS) and dihydrofolate reductase (DHFR) and is therefore a multi-target antifolate. The fact that the structural similarities of lometrexol (and LY309887, about which for that matter no structural details have been given yet) to pemetrexed disodium gave reason to combine the disclosures of the two chapters cannot be regarded as proven, simply because it is very difficult to predict a pharmaceutical effect based solely on a chemical formula. If, in addition, it is known that lometrexol and pemetrexed have different mechanisms of action, this is even less to be expected. Accordingly, the person skilled in the art would have no motivation to combine the disclosure of Chapter 8 with that of Chapter 12 from Jackman.

Even if the person skilled in the art knew that vitamin B12 was required in the methylation cycle for the conversion of 5-methyl-tetrahydrofolate (5-MTHF) to tetrahydrofolate (THF) and that tetrahydrofolate (THF) plays an important role in the DNA cycle, such that the two named cycles are linked to each other via tetrahydrofolate, he would also know that vitamin B12 is a co-factor, and thus existing vitamin B12 would not be consumed. In the presence of vitamin B12, the methylation cycle would therefore not be completely blocked. For this reason, the person skilled in the art would also by no means find motivation in his technical knowledge to supplement the teaching from Chapter 8 of Jackman in such a way that he would combine an administration of pemetrexed disodium with vitamin B12. Accordingly, the present claims 1-14 are inventive with respect to Jackman.

2.2 According to Art. 1 Para. 2 PatG, anything that is obvious having regard to the state of the art (Art. 7 para. 2) is not patentable as an invention (cf. Art. 56 EPC 2000). The state of the art

comprises everything made available to the public by means of a written or oral description, by use, or in any other way prior to the filing or priority date (Art. 7 Para. 2 PatG, Art. 54 Para. 2 EPC 2000). The state of the art not only forms the basis of the examination of novelty, but also of inventive step. According to the understanding of the person skilled in the art, documents are to be interpreted on the priority or filing date. Accordingly, not only the wording of a document is decisive, but there are also solutions in the state of the art that are obvious to the person skilled in the art due to prior publication; the content of a publication as a whole is critical. In particular, the common general knowledge of the skilled team must be taken into account, as it is accessible in particular in reference works in the relevant technical area. However, internal knowledge such as test results do not belong to state of the art (BGE 144 III 337 E. 2.2 p. 340 f.).

According to the case law, it is decisive for the assessment of inventive step whether, in view of all the partial solutions and individual contributions making up the state of the art, the person skilled in the art can arrive at the solution to the patent in suit with little intellectual effort, or whether additional inventive activity is required. This because, according to established practice, the field of inventiveness does not begin immediately beyond the known state of the art, but only beyond what an average person skilled in the art in the relevant field can further develop and find with his knowledge and skills (BGE 138 III 111 E. 2.1 p. 116 including references).

Inventive step is to be assessed from the starting situation as it objectively presented itself at the relevant point in time. No teachings are to be patented, which the person skilled in the art can consequently develop from the state of the art based on his knowledge of the state of the art and his average abilities; rather, it requires a qualitative further development, an intuitive, associative activity. The state of the art at the relevant point in time is to be considered in its entirety, in the sense of a "mosaic." To solve the problem, all of the teachings that are available to the public and all of the documents are to be regarded together as the technical expertise that was available to the skilled person or team with normal combination skills for an independent evaluation to solve the problem. The combination of individual elements from the state of the art finds however its limit where it becomes an artificial

ex post consideration with knowledge of the new solution (BGE 138 III 111 E. 2.1 p. 116 f. with references).

2.3
2.3.1 Contrary to the view expressed in the appeal, the lower court cannot be criticized for incorrectly determining the closest prior art. Rather, the citation in Chapter 8 of Jackman was correctly regarded in its entirety. By initially acknowledging that various passages of this publication contained contradictory recommendations regarding the effectiveness of a combination of pemetrexed and folic acid, and subsequently considering that the negative influence of the folic acid addition on the effectiveness was confirmed to the person skilled in the art by two further documents, the lower court did accurately consider the state of the art in its entirety. There is no evidence of a violation of federal law.

2.3.2 Appellant can also not be followed when it submits, that by taking a comprehensive view or a systematic interpretation of section 2.6 on p. 190 f. in Chapter 8 of Jackman, the skilled person would not have recognized a contradiction between the passage cited in the contested decision on p. 191 and Fig. 4 reproduced immediately afterwards on p. 192. Contrary to what Appellant appears to assume, the lower court did not conclude that there was a contradiction based on the way the publication is structured, but instead recognized a contradiction based on the different information content of each Fig. 4 and the conclusion on p. 191. It is not clear in what way the contradiction found would have been resolved by the systematic examination of the entire section as presented in the appeal and the person skilled in the art would have started from consistent recommendations.

2.3.3 Appellant is also unable to point out any violation of federal law by trying to draw conclusions from Fig. 4 that differ from the contested decision. Apart from the fact that the contested decision does not state that the person skilled in the art recognizes "from experience the problem of the toxicity of pemetrexed even when administered in very small doses" (Art. 105 Para. 1 BGG), Appellant cannot be followed if it intends to conclude from the absence of a vertical, dashed line (as shown at a dose of 3, 10 or 30 mg/kg pemetrexed with added folic acid) on the "Percent Dosage" axis when administering 0.3 mg/kg pemetrexed without folic acid, that Fig. 4 suggests both to a

layperson as well as to a person skilled in the art that deaths occur even when administering smallest doses of pemetrexed without folic acid. There is no apparent reason why the mortality should be shown with a dashed line at higher doses in the same graphic, but not when administering 0.3 mg/kg only, although mortality should also occur at this dose. Contrary to the view expressed in the appeal, it is not understandable how the person skilled in the art would extrapolate based on Fig. 4 with regard to the low dose of 0.3 mg/kg pemetrexed to a mortality associated with it, despite the lack of corresponding information, let alone to a mortality that is "significantly higher" than at an increased dose in combination with folic acid. In addition, both the effectiveness as well as the mortality according to Fig. 4 are obviously affected by the dosage, which is why the latter cannot simply be ignored; Appellant's objection that only the inhibition axis and the information on "Percent Lethality" are of importance to the person skilled in the art cannot convince.

Therefore, criticizing the lower court’s consideration according to which Respondent's argument in view of Fig. 4 is conclusive, namely that the person skilled in the art had no motivation to administer folic acid to the patient and in doing so would be forced to massively increase the pemetrexed dose in order to achieve 100% inhibition, if he had already achieved 100% inhibition at a significantly lower dose but without folic acid, is not valid.

2.3.4 In context with the motivation of the person skilled in the art to combine the disclosure of Chapter 8 with that of Chapter 12 by Jackman, which motivation was denied by the lower court, Appellant wrongly accuses the lower court of setting the threshold for non-obviousness or inventive step too low. Contrary to what Appellant appears to assume, the lower court, when considering that the fact that Chapters 8 and 12 belong to the same publication does not suggest that the person skilled in the art would have "necessarily" combined their disclosures, simply expressed that the person skilled in the art would not have combined the findings of the two contributions only because they form part of the same publication. The lower court has reasonably explained that the chapters in question were written by different authors and therefore represent independent works that in addition deal with different antifolates (lometrexol and LY309887 on the one hand and pemetrexed on the other hand), each with different properties and mechanisms of action. With its considerations, the

lower court did not place too low demands on inventive step, but correctly examined whether the person skilled in the art, having regard to the prior art and based on his average skills, could logically develop the claimed teaching from the prior art. With the general assertion that the mechanisms of action of the antifolates in question were known or that they overlap in at least one of three targets, Appellant is unable to prove the lower court consideration to be contrary to federal law, namely the consideration according to which the structural similarities of lometrexol and LY309887 to pemetrexed disodium do not provide any reason to link the disclosures of Chapters 8 and 12, because it is very difficult to predict a pharmaceutical effect based on a chemical formula alone, and this is even less to be expected due to the fact that lometrexol and pemetrexed have different mechanisms of action.

In the notice of appeal, Appellant argues indeed that the relevant passage relates generally to antifolates, but it does not indicate to what extent the lower court's consideration in the contested decision that the disclosure in question in Chapter 12 relates to antifolates other than pemetrexed (i.e. lometrexol and LY309887), is supposed to have been contrary to federal law. For this reason, Appellant's further argument that with regard to the combination with folic acid, Chapter 12 of Jackman provides exactly the same finding as Chapter 8 does, which is why the findings in Chapter 12 are applicable directly to the ones in Chapter 8, is irrelevant. In view of the differences found, the lower court's consideration that the person skilled in the art would have had no motivation to combine the disclosures of the two chapters cannot be objected to.

There is no violation of Art. 1 Para. 2 PatG (in conjunction with Art. 26 Para. 1 lit. a PatG) and Art. 56 EPC 2000 in the assessment of inventive step.

3.
The appeal must be dismissed to the extent it can be dealt with. According to the outcome of the proceedings, Appellant is liable for costs and compensation (Art. 66 Para. 1 and Art. 68 Para. 2 BGG).

Accordingly, the Federal Supreme Court recognizes:

1.
The appeal is dismissed to the extent it can be dealt with.

2.
The court costs of CHF 16,000 will be imposed on the Appellant.

3.
Appellant has to compensate Respondent for the Federal Court proceedings with CHF 18,000.

4.
This judgment will be communicated in writing to the parties and the Federal Patent Court.

Lausanne, May 1, 2020

On behalf of the 1st Civil Law Department
of the Swiss Federal Supreme Court

The President: Kiss

The Clerk: Leeman


10 JUIN 2020
SPEDIZIONE