FR – *Eli Lilly v. Fresenius Kabi*

Joining a majority of European Courts, the Paris court has held that Eli Lilly's patent, claiming the combined administration of pemetrexed disodium with vitamin B12, is infringed by the marketing of pemetrexed diacid, and it has awarded the largest ever patent infringement damages award in Europe (28,000,000 €).

***Eli Lilly v. Fresenius Kabi, tribunal judiciaire de Paris*, 11 September 2020, Docket Nº 17/10421**

Pierre Véron, Honorary President, EPLAW

On 11 September 2020, the *tribunal judiciaire de Paris* (which, from January 2020, is the new name given to the Paris first instance court, which has jurisdiction for the whole of France for patent cases) issued a major decision in the pemetrexed saga that has been litigated in more than 10 European countries.

Siding with the vast majority of judges who have decided similar cases to date, the *tribunal judiciaire de Paris* held that Eli Lilly's EP 1 313 508, relating to a combined administration of pemetrexed disodium (marketed under the brand Alimta ®) with vitamin B12 for the treatment of lung cancer, is valid and that the sale of Fresenius Kabi's pemetrexed diacid infringed the patent.

In the same judgment, the court ordered the defendants to pay 28,000,000 € as an advance payment for damages, the highest amount ever granted by a court in Europe for damages for patent infringement.

Eli Lilly was represented by Stanislas Roux-Vaillard (Hogan Lovells); Fresenius Kabi was represented by Elisabeth Berthet-Maillols (Promark).

Background

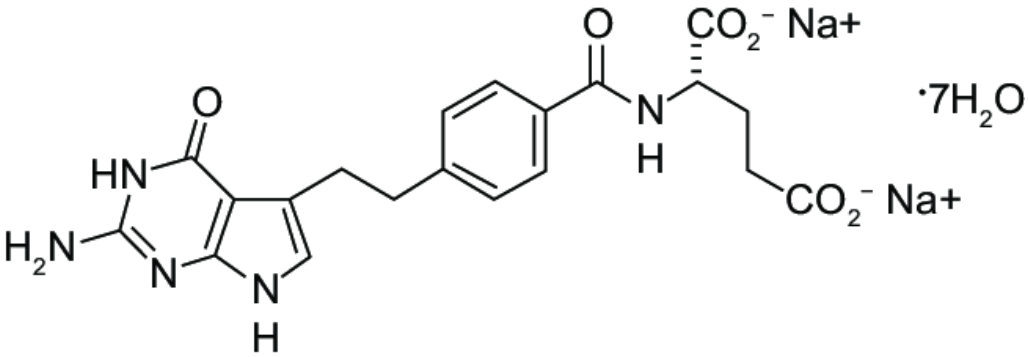
Eli Lilly's patent, EP 1 313 508, concerns the combined administration of the drug pemetrexed (marketed under the brand Alimta ®) with vitamin B12 and optionally folic acid, for treating two types of lung cancer; this combination reduces the toxicity of the active ingredient pemetrexed whilst preserving its therapeutic efficacy.

Its Swiss-type claim n° 1, as granted, reads:

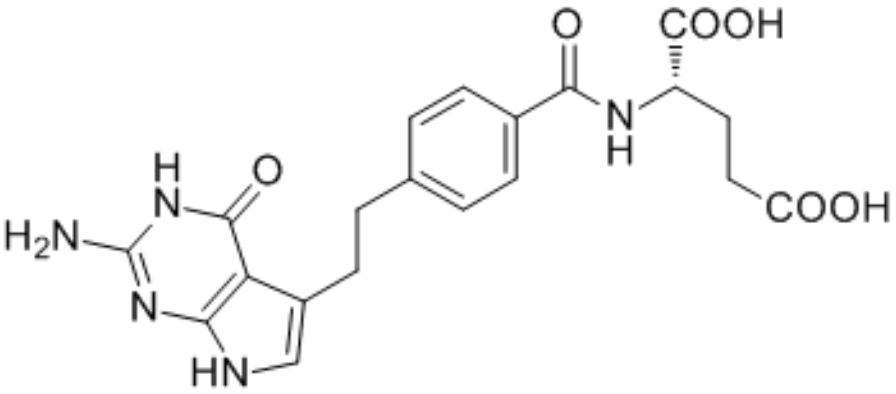
> *"1. Use of **pemetrexed disodium** in the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals, wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof, said pharmaceutical derivative of vitamin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

In France, Fresenius Kabi markets the generic version of Alimta® under the name "*Pemetrexed Fresenius Kabi*", and it is presented in the form of a diacid of pemetrexed (the sodium cations are replaced by hydrogen cations).

The following drawings illustrate the chemical structure of the patented product and of the accused product:



Eli Lilly's patent pemetrexed disodium



Fresenius Kabi's embodiment: pemetrexed diacid

Proceedings

Eli Lilly's patent, EP 1 313 508, has given rise to an unrivalled number of cases in Europe (and elsewhere).

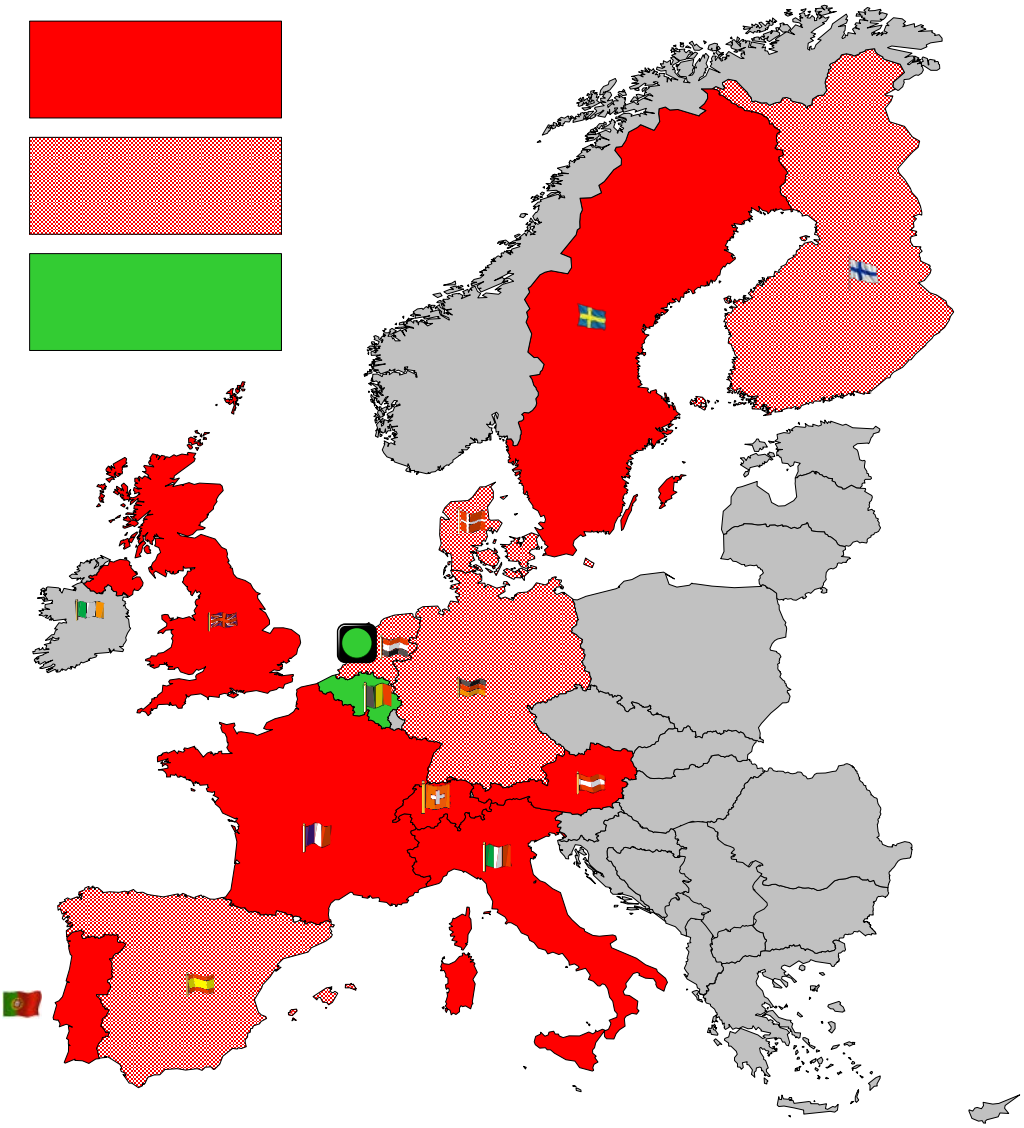
An opposition against this patent failed before the EPO.

The invalidity attacks against the patent have also failed before national courts, with the exception of a decision at first instance of the German Federal Patent Court (*Bundespatentgericht*) which declared that the German part of the patent was invalid; however this decision was overturned by the German Federal Supreme Court (*Bundesgerichtshof*) on 7 July 2020.

In other proceedings in the United Kingdom, Switzerland, Italy, Germany, Sweden, Austria, Finland, Denmark, Portugal, Spain, and the Netherlands against various manufacturers of generic versions of the drug Alimta ®, Eli Lilly has obtained interlocutory or final injunctions [the most famous judgment being the 12 July 2017 decision of the United Kingdom Supreme Court *Actavis UK Limited and others v Eli Lilly and Company ([2017] UKSC 48)* that has significantly changed the law of patent infringement in the UK].

However, on 19 June 2019, the District Court of The Hague (*Rechtbank 's-Gravenhage*) took a different view and dismissed the infringement claim:, this judgment is currently under appeal].

In Belgium, the judgment dismissing the infringement case was annulled for procedural reasons by the court of appeal, which has still to issue a decision on the merits.



Outcome of the outcome of the proceedings between Eli Lilly and generic manufacturers

Overview of the judgment handed down by the court of Paris on 11 September 2020

Besides procedural issues, which are of lesser international interest, the court decided on the scope of the patent, its infringement, its validity (a relatively unusual sequence in French judgments), and damages.

The scope of the patent: prosecution history irrelevant in this case

The court's conclusion on the scope of the patent was as follows: "*The scope of the patent extends to all pharmaceutically acceptable forms of pemetrexed (salts or others) used in combination with the two other substances.*"

To reach this conclusion, the judges restated article 69 EPC and the 1973 Protocol on the Interpretation of this article 69.

The court stressed that the technical contribution of the patent lay in the combined use of an antifolate drug, and in particular to "*the antifolate pemetrexed disodium*" with vitamin B12, and pointed out:

> *"The person skilled in the art knows that the active part of the active ingredient pemetrexed is the anion (which causes both the therapeutic effects and the adverse side effects), which is combined with vitamin B12 (and optionally folic acid), and will understand without stopping at the literal wording of the claims that the invention lies in the combined administration of the active ingredient, regardless of its form, with the other substances claimed in the patent."*

They dismissed the various arguments put forward by Fresenius Kabi:

> *"This interpretation is in compliance with the principles restated above, without it being possible to take into consideration, not only elements foreign to the patent (such as the formulation of other patents of the patent holder which, contrary to the present patent, refer to the same active ingredient and "*its pharmaceutically acceptable salts*"; the experience of the applicant in the field of patents; or even its status as a pharmaceutical company), but also elements related to the administrative granting procedure."*

Of particular interest is the court's approach to the effect of the prosecution history.

This was raised by the defendant who pointed out that the claims discussed at the EPO covered the use of "*an antifolate*":

> *"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."*

Fresenius Kabi contended that the scope of the claims was then narrowed to the use of pemetrexed:

> *"1. Use of* ***pemetrexed*** *in the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof."*

And that it was further narrowed to the use of pemetrexed disodium in the granted claims:

> *"1. Use of* ***pemetrexed disodium*** *in the manufacture of a medicament for use in combination therapy for inhibiting tumour 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".*

The defendants' arguments are disregarded by the court:

> *"Indeed, given that the patent is a self-sufficient document, the examination procedure before the Office, which can only optionally be invoked as a mere tool of interpretation, has no effect on the scope of the patent and binds neither the judge nor the patent holder. The behaviour of the patentee having complied with a request of amendment from the examiner cannot be interpreted as an admission which could be binding upon the Court and has no impact whatsoever on the scope of the claim. It does not amount to an acknowledgment or a waiver on his part, nor may it be considered as a statement, all the more so in the present case, where the company Lilly intended to refer to a preferred embodiment but without stating any intention to modify the scope of its patent, irrespective of the fact that it may not have raised any argumentation to counter the examiner, while, moreover, an amendment for addition of subject matter under Article 123 §2 of the EPC is not meant to overcome prior art that could call into question the validity of the patent, and is carried out for considerations of pure form only. The amendment for addition of subject matter is not of such nature that it could prohibit the patentee from claiming infringement by equivalents, since it is a condition of form relating to the literal content of the specification and the subject-matter of the inventive contribution, that prohibits the patentee from adding an element which could not be derived directly and unambiguously from the patent; it by no means modifies the basis on which the interpretation must be made and it has no effect whatsoever on the scope of protection conferred. On the contrary, with respect to the assessment of the scope of the patent, the aforementioned Article 69 of the EPC requires that the equivalents must be considered. It can be inferred from this that an addition of subject matter in the context of the granting procedure does not prohibit the assertion of infringement by equivalence, provided that the particular means or combination of means claimed (here the combined use, with the active ingredient, of vitamin B12 and optionally of folic acid) has a novel function (i.e., reduction of toxic effects without affecting therapeutic efficacy); otherwise, the doctrine of equivalents would be devoid of any effect."*

This leads the court to the conclusion that "*The scope of the patent extends to all pharmaceutically acceptable forms of pemetrexed (salts or others) used in combination with the two other substances*".

Direct infringement by reproduction (not by equivalence)

The court went on to discuss direct (make, use and sell) and indirect (contributory infringement, "*contrefaçon par fourniture de moyens*") infringement, either by reproduction or by equivalence.

Having reached the above conclusion on the scope of the patent, the court unsurprisingly decided that Fresenius Kabi infringed Eli Lilly's EP 1 313 508 directly by reproduction (not by equivalence):

> *"Direct infringement implies the reproduction of the essential means of the invention, i.e. those which are necessary and sufficient to ensure the primary function of the invented means, and it is acknowledged when the essential similarities are reproduced, notwithstanding secondary differences.*
>
> *In the present case, in view of the scope of the patent, and given that the formal amendment during the granting procedure does not confer any essential character on the amended element, because the granting of the patent was not conditioned to it, as was stated above, the essential means of the invention consists of the combined administration of the active ingredient pemetrexed, regardless of its form, with vitamin B12 or its other derivatives, and optionally, with folic acid or its other derivatives.*

The generic drug of Fresenius is composed of the same active ingredient, pemetrexed, and its administration must be combined, as provided by Patent EP 508, with vitamin B12 and folic acid. It matters little that the allegedly infringing compound uses a diacid solution to allow administration of this combination, since this does not produce any particular technical effect, keeping in mind that it is admitted that a specialist in formulation is capable of proposing a certain number of possible counterions other than sodium, in the form of a free acid or in the form of a certain number of well-known pharmaceutically acceptable salts. The selection of the form of the salt is therefore of no importance whatsoever, the only thing that matters being the therapeutic effect of the pemetrexed anion combined with other substances. The lack of obviousness alleged by the Defendants with respect to the use of this particular salt, classified in 10th place among frequently utilized salts, which is a criterion of validity of an invention and not a criterion of infringement, or else the fact that the company Fresenius obtained patents (EP 768 and US 9,421,207) for this form of salt, are irrelevant.

The variation related to the use of a different salt is of totally secondary importance. Pemetrexed Fresenius Kabi is administered according to the use provided for by the invention, and it is intended to treat the same cancerous diseases with the same technical effect. It was authorized as a generic drug of the reference drug.

Infringement by reproduction is established.

Given that direct infringement by reproduction is established, in consideration of the scope of the patent as determined, there is no reason to make a determination about infringement by equivalence."

It is interesting to compare the reasoning of the French court, who decided that the patent was infringed by reproduction (not by equivalence), with the reasoning of the United Kingdom Supreme Court in Actavis UK Limited and others v Eli Lilly and Company ([2017] UKSC 48) because both courts discuss the infringement of the same patent under French law.

The plaintiff, Actavis, brought an action for a declaration of non-infringement before the UK courts, requesting them to make a decision not only for the UK, but also for the territories of France, Italy and Spain; this required a consideration and application of the French, Italian and Spanish laws on infringement, respectively.

When it came to France, the UK Supreme Court agreed that the patent would be infringed under French law by the marketing of Actavis' pemetrexed diacid; in reaching this conclusion the Court referred to the French doctrine of equivalence pursuant to which a patent is infringed notwithstanding that the structure of the accused element is different from that claimed, provided that two conditions are met: firstly, the infringing element must perform the same function to achieve a similar result; and secondly the function performed by the patented means must be novel, such that it constitutes a *moyen général*, or "general means" (note that if the function is not novel, it constitutes a *moyen particulier*, or "specific means", which is infringed only when the specific structure can be seen in the accused device).

Lord Neuberger, the then President of the Supreme Court, gave the leading judgment of the UK Supreme Court in what was otherwise a unanimous opinion:

"Turning first to French law, it appears to me that the answer to the question of direct infringement ultimately turns on whether the Patent in this case falls into the moyens généraux *category or the* moyens particuliers *category, because, as discussed in para 46 above, the doctrine of equivalents is apparently only applicable to patent claims in the former category. With some diffidence, I have reached a different conclusion from Arnold J on this issue and have concluded that the Patent in this case falls into the former category.*

> *… the Patent discloses that pemetrexed disodium could be used for a function for which it could not previously have been satisfactorily or safely used in practice; specifically, that pemetrexed disodium could be used with vitamin B12 to achieve an end which could not have been achieved by either chemical on its own, pemetrexed disodium because of its harmful side-effects and vitamin B12 because it would not have worked. The essential point, as I see it, is that the Patent revealed for the first time the existence of a combined means which functioned in a certain way, namely to alleviate certain cancers without serious side-effects. It would be different if the overall function of the combination of the two chemicals had not been new."*

In a nutshell, the UK Supreme Court found that the use of pemetrexed diacid would be a direct infringement by equivalence under French law, while the French Court found that such use was a direct infringement by reproduction.

When considering the difference between these findings, in practice, it is not so great – rather than an ocean, it is more like… a Channel.

For the sake of completeness, it should be added that, having found a direct infringement, the court of Paris did not examine the claim for contributory infringement (*contrefaçon par fourniture de moyens*).

Invalidity of the patent

The French court found that there is not an extension of subject matter beyond the content of the application.

It also found that the disclosure in the patent was sufficient: "*the teachings of the patent, described and documented by tests, including those relative to the combination referred to in Claim 1 (pemetrexed and vitamin B12 alone), allow the invention to be implemented*".

On obviousness, the court reviewed two pieces of prior art (Jackman and Scott) and concluded as follows:

> *"Nothing makes it possible to conclude that the person skilled in the art, seeking to solve the specific problem of the patent, in its two branches, would have used one of any of the numerous documents cited, alone or in the combinations suggested, and would have obviously arrived at the solution provided by the patent, it being emphasised that the invention came after several decades of unsatisfactory scientific research in order to meet a need felt for a long time and that it constitutes an undeniable technical advance".*

Again, this decision is not surprising as it is in alignment with the decisions previously given on this patent by the other European courts (except the nullity decision of the *Bundespatentgericht* which, as discussed, was eventually set aside by the *Bundesgerichtshof*).

Damages and costs awards

The damages awarded in the case are of particular interest because, to the writer's knowledge, they represent the highest sum awarded for patent infringement in Europe: the court granted a preliminary total of 28,000,000 € in damages.

According to the current practice in the Paris court in such cases the defendants are ordered to present their books to the plaintiff's litigation team so that they can calculate the final amount of damages; such inspection is intended to encourage the parties to amicably settle the amount. (in the event that no agreement is reached, the court would make a decision on the final amount of damages).

Pending an inquiry on damages, the court orders the defendants to pay an advance on the damages suffered by each claimant.

The patent holder, the US company Eli Lilly, obtained an advance payment for royalties of 8,000,000 €.

The court took into account the number of vials sold by the defendants in France and calculated an increased license fee of 25% on the turnover that these sales represented:

> *"The economic damage to the company Eli Lilly, the patent holder, is evaluated based on the license fee, increased, that it could have expected if it had granted an authorization to its opponents. With respect to the number of 100 mg (20,742) and 500 mg (46,862) vials sold, as shown by the public data available from the Groupement pour l'Élaboration et la Réalisation des Statistiques [Group for the Compilation and Preparation of Statistics] (GERS) and the sales revenues thus generated, and applying an increased license fee of 25%, it appears justified to provisionally order an indemnification of 8,000,000 euros as compensation for said damage."*

The French distributor of the drug Alimta ®, the company Lilly France, obtained an advance payment of damages of 20,000,000 €, for unfair competition.

According to French case law, the distributor of a patented product, when he is not a licensee, may claim damages from the infringer on the basis of the law of unfair competition. Infringement is considered a tort which should be compensated by damages that cover the loss suffered by the distributor.

In the present case, Lilly France argued that the introduction of Fresenius Kabi's generic product to the market resulted in the health authorities cutting the price of the princeps; Lilly France claimed that it should therefore obtain damages corresponding to the price erosion that it suffered to its sales.

The court only partially accepted this reasoning:

> *"Regarding indemnification for the economic damage to the company Lilly France resulting from the acts of unfair competition, limited to lost profits, taking into account the differences between the face value published in the Official Gazette and that effectively granted after conventional and commercial discounts, and the erosion of the price of Alimta ®, which is inevitable independently of any marketing of the generic and for which the Defendants are only partially responsible, this indemnification shall be provisionally set at the sum of 20,000,000 euros."*

With regards to costs, the judgment requires the defendants to pay 350,000 € to the plaintiffs, which also may be the highest amount ever granted by the court of Paris for costs in patent infringement proceedings.