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Pemetrexed in France Act 2: 1 PI + 4 millions

Matthieu Dhenne (Dhenne Avocats) · Monday, February 8th, 2021

Readers of the Blog should remember the French landmark French judgment rendered in September 2020 in the European Pemetrexed saga, which condemned Fresenius to pay € 28 million in damages (see here). This time the action brought by Eli Lilly on French territory concerns the same drug but is directed against another generic commercialized by Zentiva. Interestingly, the action takes a different form: it is no longer an infringement action, but a request for preliminary injunction and provisional damages before the pre-trial Judge (i.e. the Judge preparing the case on the merits).

Let's quickly remind ourselves of the facts. Eli Lilly's patent EP 1,313,508 ("EP'508") relates to the combined administration of the drug pemetrexed disodium (sold under the brand name Alimta®) with vitamin B 12, and possibly with folic acid, to treat two types of lung cancer. Claim 1 reads as follows:

« *1. Use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals to which 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.* »

Pemetrexed disodium is a toxic anti-cancer agent with significant side effects. But, according to the patent, the combination with vitamin B 12 reduces this toxicity, as vitamin B 12 reduces the level of methylmalonic acid without altering the effectiveness of pemetrexed.

In 2018, Zentiva obtained marketing authorization for a generic of Alimta® – "Pemetrexed ZENTIVA" – and has been marketing this generic in France ever since. The summary of product characteristics of the said drug provides for a compulsory premedication regime according to which it must be combined with vitamin B 12, as also indicated in patent EP'508. However, ZENTIVA's medicine includes a pemetrexed diarginine and not disodium, because diarginine salt would provide greater stability to the product.

Thus, the Judge had to rule on the validity of the patent, its scope, its infringement and damages.

The Judge rejected the arguments for invalidity of the patent put forward by the defendant (absence of inventive step).

Regarding the scope of the patent, the Judge relied on Article 69 EPC – i.e. claims must be interpreted in the light of the description and drawings – and on its interpretation protocol. It was held that in this case the description referred to the general class of antifolic medicines, to which pemetrexed disodium belongs, which seemed to result from the fact that the application as filed claimed an antifolate, before its scope was limited to pemetrexed disodium. In other words, according to the Tribunal, the technical contribution of the patent lies in the combined use of an antifolic medicine, and in particular the antifolic pemetrexed disodium with vitamin B12. The invention consists essentially of the combination of pemetrexed with vitamin B12, the disodium form of the active ingredient being irrelevant. Thus, it was decided that "*the person skilled in the art* […] *fully understands that the active part of pemetrexed, disodium or otherwise, is the anion, which is at the origin of both the therapeutic effects and the undesirable side effects, independently of the sodium cations, and will understand, without stopping at the literal wording of the claims, that the invention lies in the combined administration of the active ingredient, whatever the formula chosen to make it soluble and stable, with the other substances claimed in the patent*".

Regarding the infringement, the Judge considers that the medicine marketed by Fresenius constitutes a direct infringement, because all the essential means of the invention are reproduced therein, no matter how little the modification of form, material or arrangement, by the use of a distinct salt. Indeed, ZENTIVA' generic drug is composed of the same active ingredient, pemetrexed, and its administration must be combined, as provided for in patent EP 508, with vitamin B12 and folic acid. In other words, it does not matter whether it is pemetrexed disodium or diarginine, as long as it is an antifolate combined with vitamin B12.

Apart from those added in relation to the calculation of damages, our comments are essentially in line with those already made in relation to the Fresenius case.

It must be understood that if the invention is limited to the content of the patent, the scope of its protection, on the contrary, leaves room for interpretation by the Judge. Three zones of protection have thus been identified: the direct object of the invention (strict field and rejection of equivalents); the object of the invention (median field with obvious equivalents); the inventive idea (extended field with non-obvious equivalents) . These three zones result either from a direct interpretation of the patent (direct object of the invention and object of the invention) or from an interpretation derived from the patent (inventive idea). The two antagonistic interpretations evoked by the Protocol correspond respectively to the direct object of the invention (which is strictly limited to the content of the patent) and to the inventive idea (which extends the protection largely to the inventive idea). A strictly structural reading of the claims is therefore opposed to a strictly functional reading. Knowing that in the second case, it is the inventive idea – the idea from which the structure of the invention derives – that delimits the perimeter of the protection.

Thus, when in the reported case the Judge considers that the two forms of pemetrexed result from an identical idea (using an antifolic), based on the content of the description, it clearly seems to opt for an interpretation based on the inventive idea. This position is not new in the pharmaceutical sector in French jurisprudence. Indeed, in a case concerning rosuvastatin, the Court had already decided to refer to the content of the description to exclude a given salt from the scope of the claim and deduce that there was no infringement[1]. In this case, the patent referred to a rosuvastatin active compound in the form of an acid or a non-toxic pharmaceutically acceptable salt thereof and the Court held that the defendant did not infringe because the zinc salt used by the defendant could not constitute a "non-toxic pharmaceutically acceptable salt" as claimed, in light of the description (which referred only to salts in which the cation is an alkali metal ion, an alkaline earth metal ion

or an ammonium ion).

This position is therefore not without its difficulties. In the pemetrexed cases it benefited the patentee, but the opposite solution may also prevail, as in the rosuvastatin case in 2018. In any case, if the Judge's reasoning can, as in this case, prove to be correct from a technical point of view, from a legal point of view, one cannot omit that the rules of patent law are mishandled and that the legal security they aim to create is therefore fragilized with them. Moreover, the broad scope given to the claim allows the Judge to set aside the doctrine of equivalents at the stage of the assessment of infringement. That said, on closer examination, the fact remains that the interpretation of the scope is a matter for the doctrine of equivalents, since it is a question of relying on the function of the means and not on their structure. Moreover, the English judge considered, with regard to the same medicine, that in French law there was indeed an infringement by equivalent and not a direct infringement[2]. In any event, the interpretation adopted in the reported judgment, as in the rosuvastatin case, seems very liberal. All the more so since in France, since the law of January 2, 1968, the claims set the object of protection and the description is not supposed to be a reservoir from which the patentee can draw to delimit the protection. Eventually, the reasoning adopted in rosuvastatin and pemetrexed judgments seems to draw on the description and could in the future raise serious difficulties, particularly during freedom to operate studies.

Last but not least, the Judge issued a preliminary injunction on French territory while awarding an advance of € 4,000,000 in damages. According to the current practice of the Paris Court, in this type of case, the defendants must present their books to the plaintiff so that the final amount of damages can be calculated. Pending this investigation into damages, the Court ordered the defendants to pay an advance on the damages suffered by each plaintiff.

As in the Fresenius case, with regard to the method of calculating damages, the Judge held adopted a 25% royalty rate, resulting in € 4 millions damages. Unfortunately, there is no basis for the amount of the 25% percentage, except that it is an increased rate compared to a normal one and that it had already been used in Fresenius case. Furthermore, we should note that the basis of the calculation – turnover – appears to be out of step with the French text on damages, which provides for 3 items of cumulative damage: negative economic consequences of the infringement (including the loss of profit and the loss suffered by the injured party); non-material damage; profits made by the infringer. An alternative is provided for: the court may (at the request of the injured party) award a lump sum (L. 615-7 of the French Intellectual Property Code). In this case, the fee requested from the Judge by Eli Lilly is not a lump sum. Consequently, it should not be able to rely on turnover, but only on profits, or even on loss of profit and/or non-pecuniary damage. In other words, the basis for the royalty rate may appear to be truncated since, according to article L. 615-7, it should be profits and/or loss of profit and/or non-material loss and not turnover. However, all this still seems less surprising than the impressive sum of 20 million euros awarded in the Fresenius case for unfair competition.

That said, despite the above-mentioned criticisms, I note that the trend in favor of patentees initiated by French case law in 2018 with the Novartis case (and 13 million euros provisional damages) is once again confirmed (see already here). Notice to generic manufacturers: the time for risky launches is definitely over in France – at least for now.

[1] Paris High Court, February 2, 2018, *Shionogi Seiyaku Kabushiki Kaisha, AstraZeneca & AstraZeneca UK Ltd v. Biogaran*, RG No. 16/13292.

[2] Actavis UK Limited and others v. Eli Lilly and Company, [2017] UKSC 48.

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This entry was posted on Monday, February 8th, 2021 at 6:16 pm and is filed under France, Infringement, Litigation, Patents, Pharma, Pharmaceutical patent
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