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PEMETREXED patent infringement in France: €28 million in damages for Eli Lilly (“France is back”?)

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Joining the majority of European courts, the Paris Court of Justice ruled that Eli Lilly’s patent, which relates to the combined administration of pemetrexed disodium and vitamin B12, was infringed by the marketing of Fresenius’ pemetrexed diacid. It also awarded a record amount of damages of €28,000,000: a first in Europe.

1. The pemetrexed “saga” is one of the most closely followed and resounding in European patent litigation in recent years. After several decisions, notably in the Netherlands [1], the UK [2] and Germany [3], it is now the turn of the French Court to rule in a landmark judgment. In its decision of 11 September 2020, the Paris High Court (the “Tribunal Judiciaire de Paris”) agreed with the position taken in the majority of European countries, ruling that patent EP 1,313,508 (EP 508), which relates to the combined administration of pemetrexed disodium vitamin B 12 for the treatment of lung cancer (sold under the Alimta® trademark), was infringed by the marketing of pemetrexed diacid by Fresenius Kabi. In addition, the Court awarded the plaintiff €28,000,000 in damages, a record in Europe, where this is the first time such an amount has been awarded in patent litigation.

2. The patent EP 508 invoked in this case 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. However, 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 2016, Fresenius obtained a marketing authorization for a generic of Alimta®, Pemetrexed Fresenius Kabi®, and has been marketing this generic in France since then. The summary of product characteristics provides for a mandatory premedication regime under which the drug must

be combined with vitamin B 12, as also stated in patent EP 508. However, Fresenius' drug includes a pemetrexed diacid and not a disodium (sodium cations are replaced by hydrogen cations).

3. Thus, the Paris Court was led to rule on the scope of the patent, its infringement, its validity and damages.

The Paris Court rejected the arguments for invalidity of the patent put forward by the defendant (extension of the subject matter beyond the content of the application, insufficient disclosure, and absence of inventive step) in the last instance, i.e. after having interpreted the patent and considered it to be infringed.

With respect to the scope of the patent, the Court relied on Article 69 EPC – i.e. claims must be interpreted in the light of the description and drawings – 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 knows that the active part of the active principle of pemetrexed is the anion (which is at the same time the source of the therapeutic effects and undesirable side effects), which is combined with vitamin B12 (and possibly 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 principle, whatever its form, with the other substances claimed in the patent*". It should be noted that in reaching this conclusion, the Court refers to the examination file, which constitutes an additional source of interpretation (in addition to the description and drawings).

With respect to patent infringement, the Court infers from its reading of the scope of the EP 508 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, Fresenius' 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 diacid, as long as it is an antifolate combined with vitamin B12.

4. This interpretation of the scope of the patent attracts particular attention.

According to the Protocol of Interpretation of the EPC, to which Article 69 of the EPC refers, the interpretation of the claims must avoid the pitfalls of an overly literal or extensive interpretation of the patent [4].

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) [5]. 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) [6]. 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 Court 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 rosuvastatin case, 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 [7]. The claimed patent then 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 case it benefited the patentee, but the opposite solution may also prevail, as in the rosuvastatin case in 2018. In any case, if the Court’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 thus 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. Besides, 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 [8]. 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 [9]. However, the reasoning adopted in this judgment seems to draw on the description and could in the future raise serious difficulties, particularly during freedom to operate studies.

5. Last but not least, the Court awarded €28,000,000 in damages, an amount which is, to our knowledge, a first in Europe.

According to the current practice of the Paris Court, in this type of case, defendants are required to present their books to the plaintiff, so that the final amount of damages can be calculated. Pending this investigation of damages, the Court ordered the defendants to pay an advance on the damages suffered by each plaintiff, which in this case consisted of an advance on royalties of €8,000,000.

In addition, the French distributor of the drug Alimta®, Lilly France, was awarded an advance on damages of €20,000,000 for unfair competition.

Finally, regarding costs, the judgment requires the defendants to pay €350,000 to the plaintiffs.

6. All in all, the judgment in the pemetrexed case, with the technicality of the Court’s analysis and

the amount of damages awarded, confirms the current trend towards making Paris a key location for patent litigation – particularly in the pharmaceutical sector [10] – in Europe. This is a strong message at a time when discussions are beginning on the future location of the "pharma" section of UPC's central division, which was initially to be located in London. "France is back"?

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[1] A. Sandys, Supreme Court issues ruling in Fresenius and Eli Lilly pemetrexed case, 15 June 2020, https://www.juve-patent.com/news-and-stories/cases/supreme-court-issues-ruling-in-fresenius-and-eli-lilly-pemetrexed-case/.

[2] Actavis v Eli Lilly [2017] UKSC 48 (12 July 2017).

[3] Ch. Schulze, Major win for Eli Lilly pemetrexed patent in Germany, 8 July 2020, https://www.juve-patent.com/news-and-stories/cases/supreme-court-issues-ruling-in-fresenius-and-eli-lilly-pemetrexed-case/.

[4] Voir D. Stauder, Die Entstehungsgeschichte von Artikel 69(1) EPÜ und Artikel 8(3) Straßburger Übereinkommen u?ber den Schutzbereich des Patents, GRUR Int. 1990, p. 793. – J. Pagenberg et W. Cornish, Interpretations of Patents in Europe. Application of Article 69 EPC, Carl Heymanns Verlag, Heymanns Intellectual Property, 2006.

[5] B. Geissler, Rapport Allemagne (République fédérale), in Les brevets d'invention : rédaction et interprétation, J. Boucourechliev and J.-M. Mousseron (eds), see especially nos. 36 et seq.).

[6] D. Merz, La revendication en droit européen des brevets, Juris Druck, 1982, n° 2.1.6, p. 60.

[7] TGI Paris, 2 February 2018, Shionogi Seiyaku Kabushiki Kaisha, AstraZeneca & AstraZeneca UK Ltd v. Biogaran, RG No. 16/13292.

[8] Actavis UK Limited and others v. Eli Lilly and Company ([2017] UKSC 48).

[9] See for instance TGI Paris, 9 janvier 2008, Banque Centrale c/ DSSI, RG No. 06/05848 et CA Paris, 17 March 2010, RG No. 2006/5848.

[10] We think about the case Novartis vs. Teva. See TGI Paris, 7 June 2018, RG No. 16/15196.

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