IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICALS USA, INC.,	)	
Plaintiff,	)	
v.	)	Civ. No. 14-1268-SLR
WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA AMERICAS INC., and HIKMA PHARMACEUTICALS PLC,	)	
Defendants.	)	

MEMORANDUM ORDER

At Wilmington this 9th day of October, 2014, having conferred with counsel and having reviewed the papers filed in connection with plaintiff's motion for a temporary restraining order ("TRO");

IT IS ORDERED that said motion (D.I. 5) is granted, for the reasons that follow:

1. **Background.** Plaintiff Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") has requested a TRO to preserve the status quo while the parties more fully brief (and the court considers) Takeda's motion for a preliminary injunction. Takeda is the owner of the asserted patents,[1] all of which cover methods of administering colchicine products

[1]U.S. Patent Nos. 7,964,648 ("the '648 patent"); 7,981,938 ("the '938 patent"); 8,097,655 ("the '655 patent"); 8,440,722 ("the '722 patent"); and 7,964,647 ("the '647 patent") (collectively, "the asserted patents"). The '655, '648 and '722 patents are directed to methods for administering reduced doses of colchicine for the prophylaxis of gout flares in patients who are concomitantly taking clarithromycin ('655 patent), ketoconazole ('648 patent), or verapamil ('722 patent). The '938 patent is directed to a

for the treatment of acute gout flares, as well as for concomitant administration of colchicine with other drugs for prophylaxis (prevention) of gout flares. Defendants West-Ward Pharmaceutical Corporation, Hikma Americas Inc., and Hikma Pharmaceuticals PLC (collectively referred to as "Hikma") have launched a branded product, Mitigare™, an oral single-ingredient colchicine product, "indicated for prophylaxis of gout flares in adults" (D.I. 1, ex. H at 1), and intends to launch a generic version of such as early as Friday, October 10, 2014 at a price significantly below that of Takeda's pricing structure. Although Mitigare™ has the same active ingredient, route of administration, and strength as Takeda's colchicine product (Colcrys®), Hikma did not file its application with the FDA as an ANDA. Moreover, in its proposed label, Hikma has omitted specific mention of uses for which Takeda has patent protection.

2. **Standard of review.** "The decision to grant or deny . . . injunctive relief is an act of equitable discretion by the district court." *eBay, Inc. v. MercExchange, LLC*, 547 U.S. 388, 391 (2006). The grant of such relief is considered an "extraordinary remedy" that should be granted only in "limited circumstances." *See Kos Pharma, Inc. v. Andrx Corp.*, 369 F.3d 700, 708 (3d Cir. 2004) (citation omitted). A party seeking preliminary injunction relief must demonstrate: (1) a reasonable likelihood of success on the merits; (2) the prospect of irreparable harm in the absence of an injunction; (3) that this harm would exceed harm to the opposing party; and (4) the public interest favors such relief. *See, e.g., Sciele Pharma Inc. v. Lupin Ltd.,* 684 F.3d 1253, 1259 (Fed. Cir.

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method of treating a gout flare using a specific low-dose regiment in patients already undergoing prophylactic treatment with colchicine. The '647 patent is directed to a method of treating a gout flare using a low-dose regiment of colchicine.

2011); *Antares Pharma, Inc. v. Medac Pharma, Inc.*, Civ. No. 14-270, 2014 WL 3374614, at *2 (D. Del. July 10, 2014). A request for a TRO is governed by the same general standards that govern the issuance of a preliminary injunction. *In re Cyclobenzaprine*, 2011 WL 1980610, at *1 (D. Del. May 20, 2011).

3. **Analysis.** I start with the recognition that this dispute did not proceed through the statutory regime established to vet patent infringement issues before drugs enter the stream of commerce.[2] This is so because defendants did not note the asserted patents as having any relevance to their product Mitigare™. Because the infringement analysis need not reflect the artificial construct of ANDA litigation,[3] I in turn am not confined to the principle that "section 271(e)(2)(A) lies only against a patented use that has been approved by the FDA." *Bayer Schering Parma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1319 (Fed. Cir. 2012). To put the point differently, I can consider the record in light of the realities of the marketplace in which the parties compete.

4. In this regard, as I have noted before, "off-label prescribing - the prescription of a medication in a manner different from that approved by the FDA - is legal and common." Stafford, "Regulating Off-Label Drug Use - Rethinking the Role of the FDA," The New England Journal of Medicine (April 3, 2008) ("Stafford") at 1427. *See generally Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 350-351 and n.5

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[2]35 U.S.C. § 271(e)(2).

[3]The court in *IGI Laboratories, Inc. v. Mallinckrodt LLC*, 2014 WL 1652790 (D. Del. April 22, 2014), in addressing counterclaims under 35 U.S.C. § 271(e)(2)(A), described this section "as creating a highly artificial act of infringement . . . so that courts could promptly resolve infringement and validity disputes before the ANDA applicant had engaged in the traditional statutorily defined act of infringement." *Id.* at *1 (citing *AstraZeneca Pharm. LP v. Apotex Corp.*, 669 F.3d 1370, 1377 (Fed. Cir. 2012)).

(2001). Indeed, it has been suggested that the FDA itself has a "permissive attitude toward the promotion of off-label uses of drugs." *See* Stafford at 1428. Therefore, the fact that the Mitigare™ label does not **instruct** users to perform the patented method is not dispositive. And, indeed, the label does contain relevant information regarding use of Mitigare™ with other drugs:

> Co-administration of P-gp or CYP3A4 inhibitors or inhibitors of both P-gp and CYP3A4 (e.g., clarithromycin or cyclosporine) have been reported to lead to colchicine toxicity. The potential for drug-drug interactions must be considered prior to and during therapy.
>
> Concomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-gp should be avoided if possible. If co-administration of MITIGARE™ and an inhibitor of CYP3A4 or P-gp is necessary, the dose of MITIGARE™ should be reduced and the patient should be monitored carefully for colchicine toxicity.

(D.I. 1, ex. H at 1)

5. To prove infringement, the patentee must show that the accused method meets every claim limitation either literally or under the doctrine of equivalents. *Pfizer, Inc. v. Teva Pharms., USA, Inc.*, 429 F.3d 1364, 1376 (Fed. Cir. 2005). To establish inducement, the patentee must show "direct infringement, and that the alleged infringer 'knowingly induced infringement and possessed specific intent to encourage another's infringement.'" *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010).

6. Having reviewed the record, including the claim charts prepared by Takeda (D.I. 9, exs. M, O, and P), I conclude that Takeda has carried its burden to prove a likelihood of success on the merits with respect to direct and induced infringement.[4]

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[4]Hikma has not taken any steps to challenge the validity of the asserted patents, as would be contemplated in, e.g., a Paragraph IV notice under the ANDA regime.

More specifically, prescribing and filling prescriptions (by doctors and pharmacists) and use (by patients) of Mitigare™ for prophylaxis of gout flares will directly infringe representative claims of the '655, '648, and '722 patents. Based on the listing of these patents in the FDA's Orange Book, the parties' previous litigation history related to other colchicine patents,[5] and Hikma's instructions in the product labeling for Mitigare™, I conclude that Hikma knew about the patents and that the prescription or use of Mitigare™ infringes those patents. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (a finding of specific intent is justified when the language of the accused infringer's product labeling "would inevitably lead some customers to practice the claimed method.").

7. With respect to the '938 and '647 patents, the pharmacological properties of Takeda's branded drug Colcrys® and Mitigare™ are identical. (D.I. 7, ¶ 12) Although Mitigare™ is approved for a more limited use than is Colcrys® - the latter is approved for treatment and prophylaxis of gout flares, while the former is approved only for prophylaxis - the record indicates that it is likely that some patients may use the same medication they use for prophylaxis to treat an acute gout flare when it occurs, because the dosing is similar (administration of "0.6 mg (one capsule) once or twice daily"). (D.I. 1, ex. H at 1; *see* D.I. 7, ¶¶ 10-14) Consistent with the claim chart provided by Takeda (D.I. 9, ex. S), I conclude that Takeda has carried its burden of proof to demonstrate direct infringement. Furthermore, by providing patients using colchicine for prophylaxis

[5]Takeda previously asserted several patents against Hikma relating to the concomitant administration of colchicine with other drugs for the prophylaxis of gout flares. (D.I. 9, ex. I)

of gout flares with the same 0.6 mg colchicine that is used to treat acute gout flares, with knowledge of the patents and the dosing recommendations specified by the FDA in the Orange Book, there is sufficient evidence of a specific intent on Hikma's part to induce infringement. By selling Mitigare™, Hikma is providing a 0.6 mg colchicine product to gout patients who will likely need to treat acute gout attacks and can readily do so by taking Mitigare™ consistent with the use of colchicine as recommended by the FDA and disclosed by the '983 and '647 patents. Indeed, the limited market for Mitigare™'s approved use - prophylaxis only - further demonstrates a specific intent to induce infringement, as the vast majority of gout patients using colchicine for prophylaxis also suffer acute gout flares. (D.I. 7, ¶ 13)

8. I also conclude that Takeda has carried its burden to demonstrate the remaining prerequisites for preliminary relief. There is sufficient record evidence to demonstrate that the generic launch will significantly impact Takeda's market share of colchicine products, as well as impair goodwill, pricing, and research and development efforts. (D.I. 8) Further, it is my impression that Hikma has effectively side-stepped the ANDA regime in an effort to get its generic product to market without appropriate legal underpinnings. For these reasons, the balance of hardships (maintaining the status quo for 14 days) and the public interest weigh in Takeda's favor.

9. **Conclusion.** For the reasons stated above, Takeda's motion for a temporary restraining order is granted.

IT IS FURTHER ORDERED that defendants shall maintain the status quo with

respect to the launch of their generic colchicine product as of the date of this order,[6] and may be sanctioned if they have moved forward with their launch in bad faith despite the pendency of these proceedings. A telephonic status conference shall be conducted on Tuesday, October 14 at 1:00 p.m., with counsel for Takeda initiating the call. Takeda shall take the laboring oar in preparing a more detailed form of order for review by defendants and the court.

United States District Judge

[6]In other words, if defendants have launched so that their generic product is in the stream of commerce and, ostensibly, out of their custody or control, defendants must demonstrate that they have reached out to their customers and presented this order to them in order to stay any further distribution of the generic.