UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., and MYLAN INC., Defendants.

HONORABLE JOSEPH E. IRENAS

CIVIL ACTION NO. 11-717
(JEI/KMW)

CLAIM CONSTRUCTION OPINION

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IRENAS, Senior United States District Judge, sitting by designation:

This is a patent infringement case brought under the Hatch-Waxman Act. Plaintiff Endo Pharmaceuticals Inc. ("Endo") alleges that Defendants Mylan Pharmaceuticals Inc. and Mylan, Inc. (collectively, "Mylan") have infringed U.S. Patent Nos. 5,464,864 (filed Nov. 7, 1995) (the "'864 patent"), 5,637,611 (filed June 10, 1997) (the "'611 patent"), and 5,827,871 (filed Oct. 27, 1998) (the "'871 patent"). Presently before the Court is the parties' request for claim construction. The Court held a *Markman* hearing on July 18, 2013, and now construes the disputed claim terms as set forth below.

I.

Endo is the manufacturer of Frova, which is a drug indicated for the acute treatment of migraine attacks with or without aura in adults. The active ingredient in Frova is

frovatriptan, which is the chemical 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole.

Migraines are a type of headache. They typically last anywhere from 4 to 72 hours. Migraines are often preceded by indicators, including an aura, nausea, vomiting, or sensitivity to light. Many migraine sufferers find that their migraines occur after some kind of trigger, such as stress, certain foods, or the menstrual cycle. Frova is frequently prescribed off label to treat menstrual migraines.

Although the causes of migraines are unknown, serotonin is believed to affect migraines. Serotonin works by binding to various receptors, known as 5-HT receptors, and inducing chemical reactions. The receptor pertinent to this case is the $5\text{-}HT_1$-B receptor. Frovatriptan is one of a class of drugs that treats migraines by acting on the $5\text{-}HT_1$-B receptor. Specifically, it acts as an agonist. Agonists bind to cell receptors and cause certain reactions to take place.

A critical element of frovatriptan’s effectiveness as a migraine drug is its stereochemical properties. Stereochemistry refers to a molecule’s three-dimensional configuration. Certain compounds can have the same molecular formula but different three-dimensional configurations. These molecules are called stereoisomers. A stereoisomer that is one of a pair of stereoisomers that are nonsuperimposable images of each other is

called an enantiomer. A well-known example of nonsuperimposable images is the relationship between one's right and left hand. An enantiomer is identified as being either (*R*)- or (*S*)-, depending on whether its substituents are oriented clockwise or counterclockwise after they have been arranged according to increasing atomic weight. If the enantiomer rotates plane-polarized light in either a clockwise or counterclockwise direction, it may be identified by the symbols (+) or (-). Where a compound does not have any of these designations, the name refers to the compound without regard to its three-dimensional orientation.

Compounds can also exist as a mixture of enantiomers. When a mixture contains an equal number of (*R*)- and (*S*)- enantiomers, it is known as a racemic mixture or a racemate. A compound that is a racemic mixture is preceded by the symbol (±).

The chemical form that frovatriptan takes is also relevant. Chemical compounds can exist in a variety of forms, including free base forms, salts, solvates, hydrates, salt-hydrates, and salt-solvates. In its free base form, a compound can form a salt in the presence of a suitable acid. A salt is an ionic compound that results from the neutralization reaction of an acid and a base. A solvate is a crystal that contains solvent molecules at regular intervals in its structure. When water is the solvent, the resulting solvate is known as a hydrate. A

salt-hydrate is a crystalline form of a salt that incorporates discrete water molecules as part of its crystal lattice. Frovatriptan is a salt-hydrate that is composed solely of (*R*)-entantiomers.

The claims in the patents-in-suit cover both frovatriptan's chemical structure and its use in treating migraines.[1] Mylan filed an abbreviated new drug application ("ANDA") seeking to market a generic version of Frova before Endo's patents expired. In response, Endo commenced this action for patent infringement.

The parties have identified three claims that require construction: "compound of (general) formula (I)"; "or a salt, solvate or hydrate thereof"; and "treatment of a condition wherein a 5-HT_1-like agonist is indicated." The Court construes these claims below.

II.

Claim construction is a matter of law for the Court to decide. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1319 (Fed. Cir. 2005) (en banc) (quoting

[1] The three patents-in-suit are listed in the FDA's Orange Book for Frova. In addition to these patents, Endo has two other patents listed in the FDA's Orange Book for Frova. *See* U.S. Patent No. 5,616,603 (filed May 26, 1995); U.S. Patent No. 5,962,501 (filed Dec. 23, 1996). Endo has granted Mylan a covenant not to sue on these two patents.

Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004)).

The Court begins a claim construction analysis by examining the intrinsic evidence, which includes the claims, the specification, and the prosecution history.[2] *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "A claim construction analysis must begin and remain centered on the claim language itself." *Innova*, 381 F.3d at 1116. There is a heavy presumption that a claim term conveys its ordinary and customary meaning, which "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1313. But a patentee may overcome this presumption and choose "to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.,* 175 F.3d 985, 990 (Fed. Cir. 1999); *see also Schering Corp. v. Amgen Inc.,* 222 F.3d 1347, 1353 (Fed. Cir. 2000); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979–80 (Fed. Cir. 1995), *aff'd* 517 U.S. 370 (1996).

The claims themselves and the context in which a term is used within the claims can "provide substantial guidance as to the meaning of particular claim terms." *Phillips,* 415 F.3d at

[2] The prosecution history "consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent." *Phillips,* 415 F.3d at 1317.

1314. In addition, other claims of the patent may be useful in construing a claim term, as "claim terms are normally used consistently throughout the patent." *Id.* Similarly, claims that differ from each other may provide insight into how a term should be read. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991).

After examining the claims, "it is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning." *Vitronics*, 90 F.3d at 1582. "For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims." *Markman*, 52 F.3d at 979. For this reason, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582.

Finally, the Court should also examine the prosecution history, if it is in evidence. *Phillips*, 415 F.3d at 1317. "The prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

"[I]deally there should be no 'ambiguity' in claim language to one of ordinary skill in the art that would require resort to evidence outside the specification and prosecution history." *Markman*, 52 F.3d at 986. But if the term remains unclear or unambiguous after examining the intrinsic evidence, the Court may turn to extrinsic evidence. *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1216 (Fed. Cir. 1995). "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Although extrinsic evidence is useful in determining how a person of ordinary skill in the art would understand the term, it is less reliable for the purposes of claim construction than the patent and its prosecution history. *Phillips*, 415 F.3d at 1318-19. Therefore, extrinsic evidence must be viewed within the context of intrinsic evidence. *Id.* at 1319.

III.

"compound of (general) formula (I)"

This term appears in claim 1 of the '864, '611, and '871 patents. Endo urges the Court to give "compound" its plain and ordinary meaning, while Mylan contends that "compound" means the compound's isolated enantiomers separately, as well as any mixture of those enantiomers. In essence, Endo would like

"compound" to mean any compound of formula (I) regardless of stereochemistry. Mylan, on the other hand, argues for a construction that references the compound's stereochemistry.

At oral argument, counsel for Endo represented that both parties agree that "compound" includes "all R [enantiomers] and no S to all S and no R, and every ratio in between." (Oral Arg. Tr. 127:23-24) Mylan, therefore, argues that there is no disagreement on the meaning of "compound" and that this construction should be adopted to provide clarity. Endo, on the other hand, argues that such a construction necessarily imposes limitations and that the applicants intended "compound" to be without regard to stereochemistry. The Court agrees with Endo.

The intrinsic language makes clear that "compound" does not contemplate stereochemical structure. First, the claim language itself makes no reference to stereochemistry. Second, the specifications indicate that the applicants intended "compound" to be without stereochemical limitation. Mylan argues that "[a]ll three specifications disclose that compounds of formula (I) will exist as 'optical isomers (enantiomers)' and 'racemic mixtures.'" (Def.'s Br. 6) However, the complete language of the specifications to which Mylan refers reads, "It will be appreciated that compounds of formula (I) *may* contain one or more asymmetric centres, and such compounds will exist as optical isomers (enantiomers). The invention thus includes all

such enantiomers and mixtures, including racemic mixtures, thereof." '864 Patent col.2 l.35-39; '871 Patent col.2 l.35-39; '611 Patent col.2 l.27-31 (emphasis added). Although this language clearly anticipates the compound as an enantiomer, a mixture, or a racemic mixture, it does not place any limitations on the compound's stereochemistry. Indeed, the fact that the applicants stated that compound "may" exist as an enantiomer indicates that they did not want to impose a stereochemical limitation. *See, e.g.*, *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1289 (Fed. Cir. 2006).

If a person of ordinary skill in the art had expected "compound" to include "all such enantiomers and mixtures, including racemic mixtures," this statement would be redundant and unnecessary. *See Ranbaxy*, 457 F.3d at 1290. As such, the Court construes "compound of (general) formula (I)" to refer to the formula without regard to stereochemistry. *See Pfizer Inc. v. Teva Pharm. U.S.A., Inc.*, 882 F. Supp. 2d 643, 688 (D. Del. 2012) (construing the term "4-amino-3-(2-methylpropyl) butanoic acid" as "the chemical compound 4-amino-3-(2-methylropyl) butanoic acid," meaning "the compound without limitation as to stereochemical form").

“or a salt, solvate or hydrate thereof”

This term appears in claim 1 of the ’864 patent. A similar term, “or a physiologically acceptable salt, solvate or hydrate thereof,” appears in claim 1 of the ’871 patent. Finally, claim 6 of the ’864 patent and claims 1, 8, and 9 of the ’611 patent contain the term, “or a pharmaceutically acceptable salt thereof.” The parties agree that “salt” should be construed consistently across these claims.

The crux of the parties’ disagreement over this term is whether or not it encompasses a salt-hydrate. Mylan asks the Court to construe “or a salt, solvate or hydrate thereof” as “the compound in free base form; or such compound as a salt; or such compound as a solvate; or such compound as a hydrate.” (Defs.’ Br. 7) Endo asks the Court to give the term its plain and ordinary meaning, which it argues means a compound that meets the definition of one or more of salt, solvate, or hydrate. (Pl.’s Br. 15) The evidence supports Endo’s construction.

Endo argues that a person of ordinary skill in the art would understand “salt” to include a hydrated salt, an anhydrous salt, and the salt as a solvate. (*Id.* at 16) In other words, a “salt” could be both a “salt” and a “hydrate” at the same time, and either term would cover the resulting compound. Mylan contends that the terms are exclusive and that a salt cannot

also be a hydrate and fall within the claim. (Defs.' Br. 8) The Court sees no basis for finding that "salt" does not include a salt that is also a hydrate or also a solvent. Under Mylan's construction, "salt" would be limited to anhydrous salts, and nothing in the claim language or specifications indicates that the inventors sought to limit "salt" in such a manner.

Mylan further argues that the fact that none of the thirty-two examples in the '864 and '871 patents is a salt-hydrate indicates that the applicants did not contemplate the compound existing as a salt-hydrate. But the law is clear that "even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" *Liebel-Flarsheim Co. v. Medrad, Inc.*, 385 F.3d 898, 906 (Fed. Cir. 2004) (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F3d 1313, 1327 (Fed. Cir. 2002)). No such unequivocal intent is present here.

Finally, Mylan submits that "or a salt, solvate or hydrate thereof" is a Markush group and thus must expressly indicate that the members may be used in combination. A Markush group is a list of specified alternatives set forth in a claim and is considered to be a closed group. *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005). "[A]

proper Markush group is limited by the closed language term 'consisting of.'" *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1281 (Fed. Cir. 2003). "If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim." *Id.*

According to Mylan, "[a] compound of general formula (I) which is 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, or a salt, solvate or hydrate thereof" is a Markush group because "which is" indicates a closed group.[3] (Oral Arg. Tr. 87:14-16; 88:9-89:3) Mylan cites to *Galderma Laboratories, L.P. v. Tolmar Inc.*, No. 10-0045, 2012 WL 642450, at *5-6 (D. Del. Feb. 13, 2012), in support of its position. In that case, this Court construed "pharmaceutical composition which is a gel of" as "a pharmaceutical composition in the form of a gel consisting of." *Id.* at *5. But *Galderma* is distinguishable from this case.

The *Galderma* Court based its construction on the patent's prosecution history. The applicants originally submitted claims that used open-ended language: "comprising." *Id.* at *6. After the Examiner rejected those claims and suggested the partially open language, "consisting essentially of," the applicants

[3] As Endo's counsel noted at oral argument, this language appears only in claim 1 of the '864 patent.

"submitted claims using the closed language 'which is a gel of.'" *Id.* Thus, because the applicants attempted to keep the group of ingredients open, were offered the opportunity to partially restrict the group, and chose to create a closed group, the Court found that the group was closed. In the absence of such prosecution history here, the Court is not willing to depart from the practice of requiring a Markush group to use the words "consisting of."

The Federal Circuit has made clear that in an open group, "a" means "one or more." *See, e.g.*, *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000). Accordingly, the Court adopts the following construction for claim 1 of the '864 patent: "or one or more of salt, solvate or hydrate thereof." The Court adopts the following construction for claim 1 of the '871 patent: "or one or more of a physiologically acceptable salt, solvate or hydrate thereof." Finally, the Court adopts the following construction for claim 6 of the '864 patent and claims 1, 8, and 9 of the '611 patent: "or one or more of a pharmaceutically acceptable salt thereof."

"treatment of a condition wherein a 5-HT_1-like agonist is indicated"

This term appears in claim 2 of the '864 patent, claim 1 of the '871 patent, and claim 10 of the '611 patent. The parties

disagree as to whether "treatment" includes prophylaxis or is limited to the treatment of a specific event. Endo argues that the Court should give "treatment" is ordinary and customary meaning. (Pl.'s Br. 9) Mylan, on the other hand, argues that the Court should construe the term as "treatment or prophylaxis of a condition." (Defs.' Br. 10) The Court will adopt Endo's construction.

To begin the analysis, the Court must determine what a person of ordinary skill in the art would expect "treatment" to mean. Although extrinsic evidence is usually reserved for resolving ambiguity in claim terms, the Court may consult extrinsic evidence in the absence of ambiguity to understand how a person of ordinary skill in the art would comprehend a term. *See Markman*, 52 F.3d at 986 ("Extrinsic evidence . . . may be necessary to inform the court about the language in which the patent is written. But this evidence is not for the purpose of clarifying ambiguity in claim terminology. It is not ambiguity in the document that creates the need for extrinsic evidence but rather unfamiliarity of the court with the terminology of the art to which the patent is addressed."). The Court is not "barred from considering any particular sources or required to analyze sources in any specific sequence, as long as those sources are not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Phillips*, 415

F.3d at 1324. In this case, the Court finds it useful to consult the parties' expert reports to determine the plain and ordinary meaning of "treatment."

According to the expert report of Endo's expert, Dr. Vincent P. Rocco,

> The "treatment" term . . . would be understood by one skilled in the art to mean the administration of a compound for the purpose of providing relief from a condition at the time at which that condition has presented or is expected to present. . . .
>
> . . . No one of ordinary skill in the art would understand the term "method of treatment" to mean "method of treatment and prevention." Prevention is distinct from treatment and the two should not be confused. Treatment, for instance, refers to alleviating the results of a specific event whereas prevention has a broader connotation dealing with avoiding a medical event from occurring without necessarily identifying the source of such an event (in the nature of a vaccine).

(Defs.' Ex. 4 ("Rocco Report") ¶¶ 69-70)

Mylan's expert, Dr. Stephen J. Peroutka, describes prophylactic treatment as follows: "Prophylactic treatment of migraine means routinely administering the claimed compounds regardless of the presence of headache pain—in other words, treating migraine by preventing its onset." (Pl.'s Ex. U ("Peroutka Report") ¶ 36)

Both of these descriptions demonstrate that a person of ordinary skill in the art would understand treatment to be separate from prophylaxis. Dr. Rocco clearly says that

"prevention is distinct from treatment." (Rocco Report ¶ 70) Although Mylan makes much of the fact that Dr. Rocco stated that treatment would provide relief from a condition that "is expected to present" (*id.* ¶ 69), the Court does not view this language as referring to prophylaxis. For example, as both parties have noted, migraines are often preceded by any number of symptoms, such as an aura or nausea. Thus, when a migraine sufferer experiences such a symptom, she can expect that a migraine will occur and thus take medication to treat the oncoming migraine. Or in the case of menstrual migraines, the patient could take the medication around the time each month that she would expect the migraines to present.

Prophylaxis, by contrast, would entail taking the medication in the absence of any symptoms or expectation that a migraine would occur. Dr. Petrouka's definition of prophylactic treatment is consistent with this interpretation. He states that prophylactic treatment "means routinely administering the claimed compounds regardless of the presence of headache pain." (Petrouka Report ¶ 36) This language demonstrates that prophylaxis is understood to be fundamentally different than treatment. With these definitions in mind, the Court turns to the parties' arguments.

Mylan contends that the applicants acted as their own lexicographers here and defined treatment in the specifications.

It points to the following language to support its contention: "The present invention therefore provides the use of compounds of general formula (I) . . . for the treatment of a condition where a 5-HT_1-like agonist is indicated, in particular the treatment or prophylaxis of migraine." '865 Patent, col.1 l.65-col.2 l.26; '871 Patent, col.1 l.65-col.2 l.25; '611 Patent, col.1 l.59-col.2 l.17.

A patentee may use the specifications to give a term a definition "that differs from the meaning it would otherwise possess." *Phillips*, 415 F.3d at 1316. To give a term a distinctive meaning, the patentee must show an express intent to do so. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). "[T]he written description in such a case must clearly redefine a claim term 'so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term.'" *Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000) (quoting *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999)). The applicants have not done so here. The language Mylan quotes does not show any intent – let alone an express intent – to define "treatment," and the Court will not construe "treatment" as "treatment or prophylaxis" on this basis.

Absent an express definition, the Court looks to the other intrinsic evidence. As Endo points out, the specifications clearly refer to "treatment" and "prophylaxis" separately. For example, the '864 patent states, "Currently, the most widely used *treatment* for migraine involves administration of ergtamine, dihydroergotamine, or methysergide, which are also used *prophylactically*." '864 Patent, col.1 l.14-18 (emphasis added). Another portion says, "Compounds of formula (I) . . . are expected to have utility in the *treatment and/or prophylaxis* of migraine . . . ." *Id.* col.6 l.41-44 (emphasis added). Endo contends that construing treatment as "treatment or prophylaxis" would render these specifications redundant and nonsensical.

Mylan, on the other hand, argues that the specifications actually describe using the compound in a prophylactic manner and that as such the applicants must have intended treatment to encompass prophylaxis. To support this argument, Mylan points to the following portion of the '864 patent:

> The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen . . . of the compound of the formula (I) . . . , the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example *for a week or more*.

'864 Patent, col.7 l.56-67 (emphasis added). Because migraines typically last only 4 to 72 hours, Mylan argues that this language indicates that the applicants intended the invention to

be used for prophylaxis as well as acute treatment. But this interpretation runs contrary to the meaning of treatment discussed above. This paragraph gives no indication that the invention is meant to be used absent any symptoms at all. Rather, it suggests that when used to treat a migraine or to prevent one that is expected to present, the medication should be taken for an extended period of time for effective treatment.

Because the Court can find no basis for departing from the plain and ordinary meaning, the Court construes "treatment" as treatment without prophylaxis.

IV.

For the reasons set forth above, the disputed claim terms will be construed as indicated. An appropriate Order accompanies this Opinion.

Date: August 7th, 2013

/s/ Joseph E. Irenas

Joseph E. Irenas, S.U.S.D.J.