IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN, INC., and THE SAINT REGIS MOHAWK TRIBE, *Plaintiffs,* v. TEVA PHARMACEUTICALS USA, INC., et al., *Defendants.*	§ § § § § § § § § § §	Case No. 2:15-cv-1455-WCB

FINDINGS OF FACT AND CONCLUSIONS OF LAW

BACKGROUND

The dispute in this Hatch-Waxman Act case relates to a condition known as "dry eye" and a pharmaceutical product known as "Restasis" that is intended to address that condition. Restasis is an emulsion consisting of various components, including the active ingredient cyclosporin A, an immunosuppressant, which is dissolved in castor oil, a fatty acid glyceride. Restasis, which is manufactured by plaintiff Allergan, Inc., is protected by six related patents, which will be referred to as "the Restasis patents." [1]

The defendants, Teva Pharmaceuticals USA, Inc.; Akorn, Inc.; Mylan, Inc.; and Mylan Pharmaceuticals, Inc., are generic drug manufacturers that wish to manufacture and sell

[1] Following the trial in this case, Allergan assigned all six of the Restasis patents to the Saint Regis Mohawk Tribe and received an exclusive license to the patents from the Tribe. Allergan subsequently moved to join the Tribe as a co-plaintiff. In a separate order entered today, the Court has granted that motion and added the Tribe as a plaintiff.

bioequivalent drugs having the same components as Restasis. Their principal contention is that the claims asserted by Allergan are invalid.

I. "Dry Eye" and KCS

Dry eye is a progressive condition that afflicts a substantial number of ophthalmic patients. It can cause great discomfort and sometimes leads to serious complications that can threaten the patient's eyesight. Dkt. No. 469, Trial Tr. 21; Dkt. No. 471, Trial Tr. 87-90.

In normal individuals, tears are produced naturally by the lacrimal glands above the eyes and accessory lacrimal glands in the eyelids. Dkt. No. 469, Trial Tr. 24-27. The tears form a film that covers the surface of the eye, providing protection to the eye and a smooth optical surface. The tear film in a normal individual consists of three distinct layers. The innermost layer is a mucus layer that rests directly on the cornea (the clear outer surface of the eye covering the iris and the pupil) and the conjunctiva (the tissue covering the white of the eye and lining the inside of the eyelids). The mucus layer assists the tear film in adhering to the surface of the eye. The second layer is an aqueous layer containing the tears. The topmost layer is a lipid layer produced by meibomian glands in the eyelid. The lipid layer impedes evaporation of the water from the tear film. In a normal individual, tears are produced continuously by the lacrimal and accessory lacrimal glands. The tears replenish the aqueous layer of the tear film, and then drain though tear ducts that discharge into the interior of the nose. Dkt. No. 469, Trial Tr. 24; Dkt. No. 473, Trial Tr. 32, 44.

Natural tearing serves important purposes, including providing nutrients and anti-bacterial agents to the surface of the eye and cleaning the ocular surface. The tear film also serves the important purpose of protecting the corneal and conjunctival epithelium, a thin layer of cells on the surface of the cornea and the conjunctiva. When natural tearing is inadequate (a

condition known as "aqueous-deficient dry eye"), or when the tear layer evaporates too quickly (a condition known as "evaporative dry eye"), the protective tear layer on top of the epithelium cells can be compromised, resulting in the exposure of those cells and causing damage that can be painful and can lead to adverse effects on vision. Dkt. No. 469, Trial Tr. 24-25; Dkt. No. 473, Trial Tr. 34-35. Individuals may suffer from aqueous-deficient dry eye, evaporative dry eye, or a mixture of both. Dkt. No. 473, Trial Tr. 40. The symptoms of dry eye can include a sandy or gritty feeling in the eyes, blurred vision, and infection. See U.S. Patent No. 5,981,607, col. 1, ll. 25-48.

Dry eye can be triggered by a variety of conditions. Sometimes, dry eye is caused by inflammation of the lacrimal glands or inflammation on the surface of the eye that interferes with nerve signals that would normally cause the lacrimal glands to produce tears. Dkt. No. 469, Trial Tr. 21-22, 26; see also Dkt. No. 473, Trial Tr. 34-35, 40. The condition in which dry eye is associated with inflammation and involves a deficiency in aqueous tear production is generally referred to as keratoconjunctivitis sicca ("KCS").[2] Dkt. No. 471, Trial Tr. 86-88. Evaporative dry eye can be caused by inadequate production of oil from the glands that normally replenish the lipid layer of the tear film. In a normal individual, oil in the lipid layer impedes the evaporation of tears from the surface of the eye. Dkt. No. 473, Trial Tr. 34-35, 44.

Ophthalmologists have used a variety of techniques to treat dry eye and KCS, but none has proved ideal. Frequently, ophthalmologists recommend that patients with mild to moderate

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[2] Terminology used in this field is inconsistent in various respects. In particular, different authorities define KCS differently. The Court will use the definition used in the common specification and adopted by the Court at claim construction, which is consistent with what seems to be the prevailing view among ophthalmologists today. See U.S. Patent No. 8,629,111 ("the '111 patent"), col. 2, line 63, through col. 3, line 5; Dkt. No. 214, at 3-13.

dry eye use artificial tears several times a day. Dkt. No. 469, Trial Tr. 29-30. While artificial tears provide some temporary palliative relief, they do not address the underlying conditions that cause dry eye. Other pharmaceutical treatments include corticosteroids, which address the inflammation that is often associated with dry eye, but have serious potential side effects that make long-term use problematical. Id. at 30-31; Dkt. No. 475, Trial Tr. 60-61. Non-pharmaceutical treatments have been employed, such as the use of "punctal plugs," which block the tear ducts and prevent tears from draining from the eye, thereby retaining naturally produced tears in the eye for a longer period of time; those devices, however, also come with undesirable side effects. Dkt. No. 469, Trial Tr. 30.

The evidence at trial described several common methods for diagnosing dry eye and KCS as well as methods for testing whether particular treatment regimens are effective. One commonly used diagnostic device is the Schirmer tear test. That test entails placing the end of a strip of filter paper under the patient's eyelid and measuring how many millimeters of the paper are wetted by the patient's tears within five minutes. Wetting of less than a certain amount, such as 10 millimeters on the strip, is indicative of an abnormally low amount of tear production. The Schirmer tear test can be conducted either with or without an ocular anesthetic. Conducting the test with anesthesia is considered a better test of baseline tearing, i.e., the tearing that occurs continuously and naturally in the absence of any unusual stimulation. Conducting the test without anesthesia provides a measure of baseline tearing plus "reflexive tearing," i.e., tearing that results in response to a stimulus such as an irritant in the eye, because the irritation of the paper under the eyelid tends to provoke more tearing. Dkt. No. 469, Trial Tr. 28-30. There is significant variability in Schirmer test scores depending on the circumstances in which the test is conducted, which makes assessment of those scores challenging. Dkt. No. 475, Trial Tr. 131-32.

Another commonly used diagnostic device is corneal and conjunctival staining, in which a stain is placed in the eye. Particular stains can be used that highlight dry areas on the surface of the eye or rough areas of the cornea, thus allowing the ophthalmologist to measure the degree of the patient's dry eye problem and identify areas of the cornea that have been damaged by dry eye conditions. Dkt. No. 469, Trial Tr. 26. "Rose bengal" conjunctival staining is a method to test for drying and damage to the surface of the eye and shows devitalized areas of the conjunctiva. Dkt. No. 470, Trial Tr. 72; Dkt. No. 472, Trial Tr. 25; Dkt. No. 473, Trial Tr. 37. "Fluorescein" corneal staining shows areas of superficial punctate keratitis, also known as punctate epithelial keratopathy, i.e., epithelial defects in which the outer layer of the cornea has been damaged or lost. Fluorescein staining can also be used to detect "tear break-up time," i.e., the time it takes for dry spots to appear in the tear film. Dkt. No. 469, Trial Tr. 25; Dkt. No. 473, Trial Tr. 37; Dkt. No. 474, Trial Tr. 15. Other measures of the existence of and severity of dry eye include subjective measures, such as overall discomfort levels reported by patients and specific types of discomfort, such as a sandy or gritty feeling, ocular dryness, photophobia, or a burning or stinging sensation.

II. The Development of Restasis

Allergan specializes in the development and sale of ophthalmic drugs, among other products. One of Allergan's long-term projects has been to develop products effective to treat dry eye and its symptoms. For some time, Allergan has manufactured and sold artificial tears, and in 2002, it began selling a product, Refresh Endura, that used a formulation consisting of artificial tears with 2.5% by weight castor oil added to the formulation. That product was designed to have enhanced benefits for persons suffering from dry eye or KCS, but it was not a

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