UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 1:10-cv-01376-TWP-DKL
	)	
TEVA PARENTERAL MEDICINES, INC.,	)	
APP PHARMACEUTICALS, LLC,	)	
PLIVA HRVATSKA D.O.O.,	)	
TEVA PHARMACEUTICALS USA INC.,	)	
BARR LABORATORIES, INC.,	)	
	)	
Defendants.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW FOLLOWING BENCH TRIAL AUGUST 19, 2013

This matter is before the Court for decision on the validity of claims 9, 10, 12, 14, 15, 18, 19 and 21 (the "Asserted Claims") of the U.S. Patent No. 7,772,209 (the "'209 Patent"). The '209 Patent is a method-of-use-patent which covers the co-administration of pemetrexed disodium ("pemetrexed") with two nutrients—folic acid and vitamin B12—that protect against the side effects of the drug ALIMTA®. The matter was before the Court for a bench trial beginning on August 19, 2013 and concluding on August 29, 2013. This is a Hatch-Waxman patent infringement action brought by Eli Lilly and Company ("Lilly"), the owner of the '209 Patent, against Defendants Teva Parenteral Medicines, Inc. ("Teva Parenteral"), Teva Pharmaceuticals USA, Inc. ("Teva Pharmaceuticals") (collectively with Teva Parenteral, "Teva"), APP Pharmaceuticals, LLC ("APP"), Barr Laboratories, Inc. ("Barr"), and Pliva Hrvatska d.o.o. ("Pliva") (collectively, "Defendants") arising out of Defendants' filing of Abbreviated New Drug Applications ("ANDAs") with the Food and Drug Administration ("FDA") seeking approval to market the pemetrexed disodium products identified in Teva's

ANDAs Nos. 90-352 and 90-674, APP's ANDA No. 90-384, and Barr's and Pliva's ANDA No. 91-111 (collectively the "ANDA Products") and covered under the '209 Patent.

As mentioned earlier, the '209 patent describes a method of administering a chemotherapy drug, pemetrexed, with vitamins, which is marketed by Lilly under the trade name ALIMTA®. Lilly is only asserting infringement of the Asserted Claims of the '209 Patent with respect to the ANDA Products. Each Defendant stipulates that under the Court's claim construction (Dkt. 115) and under the current laws of infringement, the sale of its ANDA Products, in accordance with the proposed labeling for each of those respective ANDA Products, would infringe the Asserted Claims of the '209 Patent, to the extent those claims are found valid and enforceable. Having heard testimony and considered the exhibits and arguments of the parties, the Court finds the Defendants have failed to show by clear and convincing evidence that the Asserted Claims of the '209 Patent are invalid for obviousness, obviousness-type double patenting, inadequate description or lack of enablement, and the Asserted Claims of the '209 Patent are valid and enforceable. In support thereof, the Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. FINDINGS OF FACT

A. The Parties

Plaintiff Lilly is a corporation organized and existing under the laws of the State of Indiana, having its corporate offices and principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285. Lilly is engaged in the business of research, development, manufacture and sale of pharmaceutical products throughout the world. Lilly sells pemetrexed in the United States under the trademark ALIMTA® for treatment of specific types of lung cancer and mesothelioma. ALIMTA® is covered under U.S. Patent No. 5,344,932, which is owned by The Trustees of Princeton University and licensed exclusively to Lilly.

The Defendants are all corporations primarily engaged in the business of making and selling drugs in generic form. Defendant Teva Parenteral is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 19 Hughes, Irvine, California 92618. Defendant Teva Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. Defendant APP is now Fresenius Kabi USA, LLC, a Delaware limited liability company with its principal place of business at Three Corporate Drive, Lake Zurich, Illinois 60047. Defendant Barr is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. Defendant Pliva is a limited liability company organized and existing under the laws of the Republic of Croatia with its principal place of business at Prilaz baruna Filipovica 25, 10000 Zagreb, Croatia.

B. The Patent-In-Suit

The patent-in-suit U.S. Patent No. 7,772,209, was issued to Lilly on August 10, 2010, and Lilly is the current owner of the '209 Patent. The '209 Patent covers the method of administration of ALIMTA®, requiring that physicians co-administer the drug with folic acid and vitamin B_{12} to reduce the incidence of patient toxicity caused by ALIMTA®.

C. History of Lilly's Antifolate Development Prior to the '209 Patent

1. Background on Antifolates

The '209 Patent describes a method of using an antifolate, pemetrexed, with vitamins. Antifolates are a type of chemotherapy drug used to treat certain types of cancer. Antifolates work by competing with folates, a class of essential nutrients that includes folic acid. Folates participate in chemical reactions in the body that make chemical precursors to DNA. DNA, in turn, is required for division and growth of both normal cells and cancer cells. Antifolates work

by interfering with the action of folates and deprive cancer cells of the DNA precursors they need to proliferate, or grow. Antifolates are used for their antiproliferative effect in the treatment of cancer to inhibit cell growth and division, which causes cancer cells to die. Because of the competitive relationship between folates and antifolates, the ability of an antifolate to fight cancer depends on the relative amount of folate and antifolate in the cell. As folate levels are increased, greater amounts of antifolates are needed to achieve an antiproliferative effect.

Cancer cells are fast-growing and thus have a high demand for DNA precursors, making them particularly susceptible to the effects of antifolates. However, fast growing normal cells, such as cells that line the gastrointestinal tract and cells of the bone marrow, also divide rapidly and are therefore also particularly susceptible to antifolates. Accordingly, the same mechanisms by which antifolates kill cancer cells also kill fast-growing normal cells, causing antifolate-related side effects referred to as "toxicities." Some of these toxicities – such as mucositis, anemia and low white blood cell counts– can be severe and even life-threatening.

Antifolate research began in 1948 with observations by Dr. Sidney Farber ("Dr. Farber") of children with leukemia. The children were given folic acid contained in liver extract, which Dr. Farber observed caused their tumor growth to accelerate. Based on that finding, Dr. Farber administered an experimental antifolate called aminopterin, which caused some of his patients to go into remission. Between 1950 and 1999, a great number of antifolates were made and tested, but as of 1999 the only antifolate approved by the FDA for treating cancer was methotrexate, which was approved in the 1950s. Methotrexate is also used in the treatment of rheumatoid arthritis ("RA"). Both cancer and RA patients experience toxicity from antifolates due to their antiproliferative effects – *i.e.* by killing rapidly dividing cells. However, unlike in cancer treatment, this antiproliferative effect is not the mechanism by which methotrexate treats RA.

2. Lilly's antifolate research and development in the 1990s

In the 1990s, Lilly had multiple antifolates in clinical use or development, including pemetrexed, lometrexol, and LY309887 (the "'887 compound"). In a few instances, researchers attempted to use folic acid pretreatment with antifolates in order to reduce the toxicities of the drug. Initial clinical trials of lometrexol, without any supplementation, were considered a "complete disaster" resulting in "appalling toxicities." Calvert Dep. Tr. 92:8-14. In an effort to address these severe toxicities, researchers tried administering lometrexol with folic acid. A Phase I clinical trial was conducted by Laohavinij[1] in 1996, which involved administering a daily oral dose of 5 mg of folic acid seven days before and seven days after lometrexol administration. TX 1036. However, the Laohavinij study of lometrexol with folic acid pretreatment reported only one response among folic acid supplemented patients, which was fewer than had been observed in earlier unsupplemented patients. TX 1036 at 333. Lilly had also pursued clinical development of a related antifolate, the '887 compound, which was also tested with folic acid pretreatment for the same reason as lometrexol, but as with lometrexol, those studies that attempted to reduce toxicity with folic acid supplementation proved unsuccessful due in part to the decrease in efficacy. In 1994, Lilly obtained U.S. Patent No. 5,217,974 (the "'974 Patent"). The '974 Patent claimed the use of folic acid pretreatment with a class of antifolates, with the preferred antifolate being lometrexol. TX 916.

One of the antifolate drugs Lilly had in development during the 1990s was pemetrexed. By the late 1990s, pemetrexed was viewed as a very promising anticancer drug. In April 1999, it was reported that phase II studies showed responses in six different tumor types, and the activity of the drug was considered "remarkable and unusual in a new drug of any class at this stage of

[1] Laohavinij, et al., *A Phase I clinical study of the antipurine antifolate lometrexol (DDATHF) given with oral folic acid*, INVESTIGATIONAL NEW DRUGS, 14: 325-335 (1996) (TX1036).

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