United States Court of Appeals for the Federal Circuit

AMERIGEN PHARMACEUTICALS LIMITED,
Appellant

v.

UCB PHARMA GMBH,
Appellee

2017-2596

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01665.

Decided: January 11, 2019

WILLIAM HARE, McNeely Hare & War LLP, Princeton, NJ, argued for appellant. Also represented by SHYAM DIXIT, Dixit Law Firm, Tampa, FL.

JEFFREY J. OELKE, Fenwick & West, New York, NY, argued for appellee. Also represented by RYAN JOHNSON, LAURA MORAN, JAMES TRAINOR.

Before LOURIE, CHEN, and STOLL, *Circuit Judges.*

LOURIE, *Circuit Judge.*

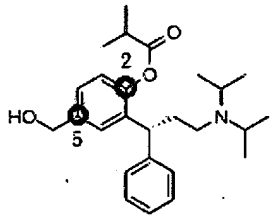
Amerigen Pharmaceuticals Limited ("Amerigen") appeals from the decision of the United States Patent and Trademark Office Patent Trial and Appeal Board (the "Board") in an *inter partes* review ("IPR") holding that claims 1–5 and 21–24 of U.S. Patent 6,858,650 (the "'650 patent") are not unpatentable as obvious. *Mylan Pharm. Inc. v. UCB Pharma GmbH*, No. 2016-00510 (P.T.A.B. July 19, 2017) ("*Decision*"). We conclude that the Board did not err in its conclusions and affirm.

I. BACKGROUND

A.

UCB Pharma GmbH ("UCB") owns the '650 patent, which covers certain chemical derivatives of 3,3-diphenylpropylamines, including a compound called fesoterodine. Fesoterodine is an antimuscarinic drug marketed as Toviaz® to treat urinary incontinence.

The chemical structure of fesoterodine is depicted below:



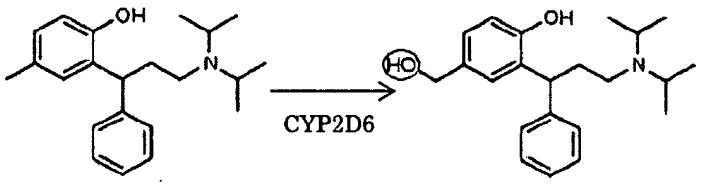
Fesoterodine

On the upper left hand benzene ring above, we will refer to the position of the hydroxymethyl group as the 5-position, and the position of the isobutyryl ester as the 2-position.

Fesoterodine is a prodrug. Unlike a typical drug, a prodrug is an inactive molecule as-delivered and requires transformation within the body into its active therapeutic form. A prodrug may be employed when administering the active molecule itself is infeasible because of poor

bioavailability (*i.e.*, the fraction of a drug dose that is absorbed into the bloodstream) or other drug delivery problems.

Fesoterodine is a prodrug of the active compound 5-hydroxymethyl tolterodine ("5-HMT"). 5-HMT is a metabolite of the compound tolterodine, an older antimusarinic drug sold under the trade name Detrol® to treat overactive bladder. In the body, tolterodine is converted to 5-HMT by cytochrome P450 2D6 ("CYP2D6"). The metabolite 5-HMT, like tolterodine, has antimuscaranic activity and thus contributes to the therapeutic effect of tolterodine. Such metabolites are known as active metabolites. The chemical structures of tolterodine and 5-HMT are shown below:



Tolterodine 5-HMT

As depicted, CYP2D6 converts the methyl group at the 5-position of tolterodine to a hydroxymethyl group in 5-HMT. Fesoterodine, on the other hand, differs from 5-HMT at the 2-position: 5-HMT has a hydroxy group, while fesoterodine has an isobutyryl ester. The issue before us is whether it would have been obvious to modify the 2-position hydroxy group of 5-HMT to an alkyl ester of six carbons or less as in fesoterodine.[1]

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[1] Claim 1, the broadest of the challenged claims, encompasses a genus of esters including "C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, [and] substituted or unsubstituted phenyl." '650 patent col. 23 ll. 30–31. The parties and the Board

B.

Mylan Pharmaceuticals Inc. petitioned for IPR of the '650 patent, and the Board instituted review of claims 1–5 and 21–24 on two grounds: (1) obviousness over the Detrol Label,[2] Postlind,[3] Bundgaard,[4] Bundgaard PCT,[5] and Berge[6]; and (2) obviousness over Brynne,[7] Bundgaard, Bundgaard PCT, and Johansson.[8] After institution, Amerigen and two other companies were joined as parties to the proceeding. Only Amerigen has appealed.

1.

The references fall into three general categories. First, the Detrol Label, Postlind, and Brynne discuss tolterodine and its metabolism and pharmacokinetics. Second, Bundgaard and Bundgaard PCT focus on prodrug design principles. Third, Berge and Johansson relate to

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focused on the motivation to make the claimed alkyl ester, which we do as well.

[2] Detrol® Prescribing Information (1998).

[3] Hans Postlind et al., *Tolterodine, a New Muscarinic Receptor Antagonist, Is Metabolized by Cytochromes P450 2D6 and 3A in Human Liver Microsomes*, 26 Drug Metabolism & Disposition 289 (1998).

[4] Hans Bundgaard, *Design of Prodrugs* (1985).

[5] International Application WO 92/08459.

[6] Stephen M. Berge et al., *Pharmaceutical Salts*, 66 J. Pharm. Sci. 1 (1977).

[7] Niclas Brynne et al., *Influence of CYP2D6 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Tolterodine*, 63 Clinical Pharmacology & Therapeutics 529 (1998).

[8] International Application WO 94/11337.

pharmaceutical salts. We will summarize each group in turn.

The Detrol Label discloses the structure of tolterodine and its metabolism to 5-HMT via the enzyme CYP2D6. The metabolite 5-HMT is reported to have antimuscarinic activity similar to tolterodine and contribute to tolterodine's therapeutic effect. The Detrol Label taught that a subset of the population (known as "poor metabolizers") lacks CYP2D6 activity and instead metabolizes tolterodine by means of the enzyme CYP34A. Since the CYP34A pathway metabolizes tolterodine more slowly than CYP2D6, poor metabolizers have higher concentrations of tolterodine and negligible concentrations of 5-HMT. However, because the sum of unbound tolterodine and 5-HMT concentrations is similar in extensive (*i.e.*, patients with normal CYP2D6 activity) and poor metabolizers, the Detrol Label teaches that the net therapeutic activity of tolterodine would be similar between both groups.

Brynne is a research paper that describes the influence of patients' varying CYP2D6 activity on tolterodine activity. Like the Detrol Label, Brynne posits that "the CYP2D6 polymorphism does not appear to be of great importance in the antimuscarinic effect, probably because of the additive action of parent drug and active metabolite." J.A. 301. However, Brynne did observe that "[t]olterodine is tenfold more lipophilic than 5-HM[T], and consequently tolterodine penetrates membranes more rapidly." J.A. 310. The reference suggests that this difference might contribute to poor metabolizers experiencing a slightly worse side effect than extensive metabolizers. But ultimately, Brynne concludes that the variation in CYP2D6 activity between poor and extensive metabolizers "does not appear to be of great pharmacodynamic importance." *Id.*

Postlind, another published research paper, focuses on tolterodine metabolism. J.A. 296. Postlind cautions

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