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Paper No. 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ROXANE LABORATORIES, INC.,
Petitioner,

v.

VANDA PHARMACEUTICALS INC.,
Patent Owner.

Case IPR2016-00690
Patent 9,138,432 B2

Before RAMA G. ELLURU, SHERIDAN K. SNEDDEN, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Roxane Laboratories, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claim 1 of U.S. Patent No. 9,138,432 B2 (Ex. 1001, "the '432 patent"). Paper 2 ("Pet."). Vanda Pharmaceuticals Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of the challenged claim. Accordingly, the Petition is denied.

A. Related Proceedings

The '432 patent is at issue in a number of cases in the United States District Court for the District of Delaware including *Vanda Pharm. Inc. v. Roxane Labs., Inc.*, No. 15-cv-00919 (D. Del.). Pet. 2–3; Paper 3, 1; Paper 6, 2.

The '432 Patent is a continuation of U.S. Patent Application No. 14/060,978, a continuation of U.S. Patent Application No. 11/576,178, which was issued as U.S. Patent No. 8,586,610 ("the '610 Patent"). The '610 Patent is at issue in the United States District Court for the District of Delaware, including in *Vanda Pharm. Inc. et al. v. Roxane Labs., Inc.*, Nos. 13-cv-01973, 14-cv-00757 (D. Del.). Ex. 1001; Pet. 3; Prelim. Resp. 33; Paper 3, 1; Paper 6, 2–3.

B. The '432 Patent and Relevant Background

The '432 patent, entitled "Methods for the Administration of Iloperidone," is generally directed to methods for lowering the risk for QT prolongation associated with the administration of iloperidone patients with lower than normal CYP2D6 activity arising from a patient's genetic background, or by the concomitant administration of a CYP2D6 inhibitor, such as fluoxetine. Ex. 1001. According to the Specification, iloperidone has antipsychotic activity that renders it useful in the treatment of "all forms of schizophrenia." *Id.* at 1:42–55. The Specification explains, however, that iloperidone or its metabolites have been associated with the prolongation of the electrocardiographic QT interval ("QTP")[1]—an adverse event associated with the potentially fatal cardiac arrhythmias including "Torsades de Pointes." *Id.* at 1:56–58; Pet. 44; Prelim. Resp. 8, Ex. 1003 ¶ 97; Ex. 2001 ¶ 46.

The '432 Specification discloses that the metabolism of iloperidone depends largely on the P450 enzymes CYP2D6 and CYP3A4. Ex. 1001, 4:46–48. CYP3A4 converts the parent drug to the active metabolite p88, which is subsequently degraded by CYP2D6. *Id.* at 2:53–55; 6:63–64. CYP2D6 also metabolizes iloperidone to p94, which is converted to P95 "after some additional reactions." *Id.* at 4:48–50. Thus, both CYP2D and CYP3A4 play a role in the metabolic clearance of iloperidone.

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[1] For convenience, we employ "QTP" to refer to all variants of the term "prolongation of the QT interval" or "QT prolongation." "QT interval" refers to the time between the Q and T waves in an electrocardiogram tracing and encompasses the term "QTc," which indicates that a QT interval measurement has been mathematically corrected for a patient's heart rate. *See e.g.*, Ex. 1001, 2:40–48; Pet. 5, n.2; Prelim. Resp. 8.

According to the Specification, the two main metabolites of iloperidone, P88 and P95, have different pharmacological effects. *Id.* at 4:54–62. Whereas "P88 has a pharmacological profile including affinity for the HERG channel similar to that of iloperidone," P95 has a "very low affinity for the HERG channel" and "is regarded being pharmacologically inactive." *Id.* By way of background, HERG channels are voltage-gated ion channels associated with QTP and cardiac arrhythmias. Ex. 1016, 151–154; *see also* Prelim. Resp. 14 (stating that, as of the time of the invention, QTP induced by drugs other than iloperidone "ha[d] been linked to inhibition of the hERG channel, a cardiac potassium channel . . . that helps regulate the heart rate") (citing Ex. 2001 ¶ 47).

The Specification discloses a series of studies evaluating blood levels of iloperidone and its major metabolites in patients with varying levels of endogenous CYP2D6 activity (e.g., patients with genotypically high and low CYP2D6 levels), including before and after the coadministration of CYP2D6 and CYP3A4 inhibitors. Ex. 1001, 2:32–11:14. The Specification discloses that "[a]ddition of the CYP2D6 inhibitor[,] fluoxetine, along with iloperidone[,] resulted in increases of the area under the curve (AUC) for iloperidone and P88 of 131% and 119% respectively," whereas, "[a]ddition of the CYP3A4 inhibitor ketoconazole . . . resulted in a 38-58% increase in the concentrations of iloperidone and its main metabolites P88 and P95." *Id.* at 4:51–57.

Levels of iloperidone and its main metabolites in subjects were also compared to changes in the QT interval. Statistical analyses showed that increased levels of the parent drug and the active P88 metabolite were associated with increased risk of QTP. *See, e.g., id*. at 10:9–10 ("QTc prolongation is correlated to the ratios of P88/P95 and

iloperidone+P88)/P95.”). Because decreased CYP2D6 activity results in increased amounts of the active moieties, iloperidone and P88, as compared to the inactive metabolite, P95, which ratios correlate with the risk of QT prolongation, the Specification recommends decreasing the dose of iloperidone in patients having reduced CYP2D6 activity due to either genetic background or concomitant treatment with CYP2D6 inhibitors. *See e.g.*, *id.* at 2:20–26, 2:65–3:3, 11:46–52. Also with respect to the concomitant treatment of iloperidone with CYP2D6 inhibitors such as fluoxetine, the Specification further discloses that “[a]nother aspect of the invention is a method for obtaining regulatory approval for the administration of iloperidone based, in part, on labeling that instructs the administration of a lower dose if the patient is already being administered a CYP2D6 inhibitor, e.g., paroxetine, etc.” *Id.* at 14:34–38.

C. Challenged Claim

Claim 1, the sole claim of the ’432 patent recites:

> 1. A method of decreasing a risk of QT prolongation in a patient being treated for schizophrenia with iloperidone, the method comprising:
>
> administering to the patient a dose of iloperidone that is 24 mg/day if, and because, the patient is not being treated with fluoxetine; and
>
> administering to the patient a dose of iloperidone that is 12 mg/day if, and because, the patient is being treated with fluoxetine.

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