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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LTD. and LUPIN PHARMACEUTICALS, INC.,
Petitioners,

v.

HORIZON THERAPEUTICS, INC.,
Patent Owner.

Case IPR2016-00829
Patent 9,095,559 B2

Before TONI R. SCHEINER, LORA M. GREEN, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

I. Introduction

We instituted a trial under 35 U.S.C. § 314 to review challenges brought by Lupin Ltd. and Lupin Pharmaceuticals, Inc. ("Lupin" or "Petitioner") against claims 1–15 of U.S. Patent No. 9,095,559 B2 (Ex.

1001) ("the '559 patent") in the Petition (Paper 3 ("Pet.")). *See* Paper 13 (Institution Decision ("DI")).

Horizon Therapeutics, Inc. ("Horizon" or "Patent Owner") filed a preliminary response under 37 C.F.R. § 42.107 (Paper 9 ("Prelim. Resp.")) and a response under 37 C.F.R. § 42.120 (Paper 26 ("PO Resp.")) to Lupin's challenges and Lupin filed a Reply (Paper 31 ("Reply")).

Lupin also filed a motion to exclude Horizon Exhibits 2019 and 2041 (Paper 35). *See also* Patent Owner's Opposition to Petitioner's Motion to Exclude (Paper 37) and Petitioner's Reply in Support of Its Motion to Exclude Evidence (Paper 38). These exhibits are discussed in footnotes below.

Horizon does not seek to amend its challenged claims under 37 C.F.R. § 42.121.

A hearing was held on July 28, 2017, and a transcript of the oral argument was made of record (Paper 41).

We conclude that the challenged claims are unpatentable under 35 U.S.C. § 103 over the cited prior art.

A.

Both Lupin and Horizon report that Horizon served Lupin with a complaint in the District Court for the District of New Jersey (Case No. 1:15-cv-07624) alleging that Lupin infringed the '559 patent, as well other related patents. Pet. 7; Prelim. Resp. 2.

Lupin also reports that U.S. Patent No. 8,404,215, which issued from the parent application of the '559 patent, was the subject of IPR2015-01127, filed by Par Pharmaceutical, Inc., and IPR2016-00284, filed by Lupin, which was instituted and joined with the IPR2015-01127 proceeding. The claims

challenged in that review are similar to the claims challenged in the present review, wherein fasting blood ammonia levels are measured, compared to the upper limit of normal, and an adjusted dose of drug is administered if "the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level." *See Par Pharm., Inc. v. Horizon Therapeutics, LLC*, Case IPR2015-01127, slip op. at 6–7 (PTAB September 29, 2016) (Paper 49). Those claims were held to be unpatentable.

Lupin reports further that IPR2015-01117 and IPR2016-00283, involving Horizon's U.S. Patent 8,642,012[1], were instituted and joined. That patent is not related by lineage to the '559 patent and it was held that Petitioner did not show that the challenged claims were unpatentable. *See Par Pharm., Inc. v. Horizon Therapeutics, LLC*, Case IPR2015-01117 (PTAB November 3, 2016) (Paper 53).

We note that Lupin has recently filed petitions for review of the claims of U.S. Patent Nos. 9,254,278 and 9,326,966 (IPR2017-01159 and IPR2017-01160, respectively), which are related as being issued from continuations of the application from the currently challenged '559 patent.

In addition, on July 13, 2017, Par Pharmaceutical, Inc. filed petitions for review of U.S. Patent Nos. 9,095,559, 9,254,278, and 9,326,966 (IPR2017-01768, IPR2017-01767, and IPR2017-01769, respectively).

Decisions on whether to institute trial based on these pending petitions has not yet been issued.

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[1] The application that became U.S. Patent 8,642,012 was published as U.S. Patent Publication 2010/0008859, which was cited as prior art in Petitioner's challenges. *See* Ex. 1007.

B.

The claims of the '559 patent are directed to methods of using a drug, glyceryl tri-[4-phenylbutryate] ("HPN-100"), to treat subjects with urea cycle disorders. Individuals suffering from urea cycle disorders ("UCDs") are unable to remove excess nitrogen waste, which is normally excreted in the urine. Ex. 1002 ¶ 30; Ex. 2006 ¶¶ 31–32. When the body functions normally, dietary amino acids are converted first to ammonia and then to urea in the urea cycle and, finally, excreted in the urine. Ex. 1002 ¶ 31; Ex. 2006 ¶ 31. In individuals with UCDs, the enzymes controlling the urea cycle are deficient, leading to high levels of ammonia in the blood. Ex. 1002 ¶ 32; Ex. 2006 ¶¶ 32–33. This accumulation of ammonia at high concentrations in the body is toxic. Ex. 1002 ¶ 32; Ex. 2006 ¶ 33. Patent Owner's witness, Dr. Gregory M. Enns[2], testifies that "[i]ncreased blood ammonia levels manifest mainly as central nervous system dysfunctions such as stupor, convulsions, and coma." Ex. 2006 ¶ 33.

The claims of the '599 patent are directed to methods wherein HPN-100 is administered at an initial or increased dose when a patient's fasting

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[2] Dr. Enns testifies that he is a Professor at the Stanford University School of Medicine. Ex. 2006 ¶ 8. Dr. Enns also testifies that he is Board Certified in Clinical Genetics and Clinical Biochemical Genetics by the American Board of Medical Genetics and Genomics. Ex. 2006 ¶ 7. Dr. Enns testifies that he has cared for approximately 70 to 100 UCD patients over the course of his career and that for the UCD patients he manages he prescribes nitrogen scavenging medications on nearly all patients who have not undergone liver transplantation. Ex. 2006 ¶ 11. To manage the care of his patients, Dr. Enns testifies that he adjusts the dose of nitrogen scavenging medication as well as tailors dietary treatment and provides emergency management. Ex. 2006 ¶ 11. We find Dr. Enns to be qualified to provide opinions on the subject matter at issue.

plasma ammonia level is less than the upper limit of the normal range for ammonia, but greater than half that upper limit.

Claim 1 of the '559 patent is representative of the claims challenged in Petitioner's Ground 1 and recites:

> A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and *who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level*, the method comprising:
>
> (a) measuring a fasting plasma ammonia level for the subject;
>
> (b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and
>
> (c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage *if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level*.

Ex. 1001, 24:28–39 (emphasis added). Independent claim 2, the only other independent claim challenged in Ground 1, is similar to claim 1, differing in the preamble among other small differences.

Claim 3 is challenged in Petitioner's Ground 2 and recites:

> A method of administering glyceryl tri-[4-phenylbutyrate] to a subject having a urea cycle disorder, the method comprising:
>
> (a) measuring a first fasting plasma ammonia level for the subject:
>
> (b) comparing the first fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and
>
> (c) administering an initial dosage of glyceryl tri-[4-phenylbutyrate] to the subject if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level and less than the upper limit of normal for plasma ammonia level.

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