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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH,
Patent Owner.

Case IPR2016-01564
Patent 8,846,695 B2

Before TONI R. SCHEINER, BRIAN P. MURPHY, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

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

INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–4 of U.S. Patent No. 8,846,695 B2 ("the '695 patent," Ex. 1001). Paper 2 ("Pet."). Boehringer Ingelheim International GmbH ("Patent Owner") timely filed a Preliminary Response. Paper 11 ("Prelim. Resp."). We review the Petition under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–4, we institute an *inter partes* review of the challenged claims.

Related Proceedings

Patent Owner informs us that it has asserted the '695 patent against Petitioner in *Boehringer Ingelheim Pharm. Inc. v. Mylan Pharm. Inc.*, Case No. 1:15-cv-00145 (N.D.W.Va.), which is currently inactive. Paper 7, 3.

According to the parties, the '695 patent is the subject of several other cases in district courts, which have been consolidated into *Boehringer Ingelheim Pharm. Inc. v. HEC Pharm Group*, Case No. 3:15-cv-05982 (D.N.J.). Pet. 5; Paper 7, 2–3. In that case, Patent Owner also asserted U.S. Patent Nos. 8,673,927, 8,853,156, and 9,173,859. Pet. 5. Petitioner has concurrently filed IPR2016-01563, IPR2016-01565, and IPR2016-01566, challenging those patents respectively. *Id.*

The '695 Patent

The '695 patent is directed to "certain DPP-4 [dipeptidyl peptidase 4] inhibitors for improving glycemic control, such as e.g. improving hemoglobin A1c (HbA1c) and/or fasting plasma glucose (FPG), in type 2 diabetes patients with inadequate glycemic control despite therapy with metformin, as well as to the use of these DPP-4 inhibitors in antidiabetic therapy." Ex. 1001, 1:6–11.

The '695 patent states that metformin is the drug of choice for beginning or first-line antidiabetic therapy. *Id.* at 2:1–7. It is, however, associated with a high secondary failure rate, that is, some diabetic patients may fail to achieve or maintain glycemic control over time. *Id.* at 1:26, 2:10–12.

"DPP-4 inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus." *Id.* at 3:67–4:3. According to the '695 patent, the inventor surprisingly found that certain DPP-4 inhibitors had "unexpected and particularly advantageous properties, which make them particularly suitable for improving glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin alone." *Id.* at 9:9–14. Specifically, the '695 patent identifies DPP-4 inhibitor 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, also known as BI 1356 or linagliptin, as particularly preferred. *Id.* at 17:33–37, 21:4–7.

Illustrative Claims

Among the challenged claims, claims 1 and 2 are independent. Claim 1 is representative and it reads as follows:

> 1. A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin, said method comprising orally administering 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine to said patient in an amount of 5 mg per day in combination with metformin.

Claim 2 is similar to claim 1, except it recites administering linagliptin "as add-on combination with metformin."

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds, each of which challenges the patentability of claims 1–4:

Ground	Basis	References
1	§ 103	Charbonnel[1] or Hughes[2] in view of the '940 Publication[3]

[1] Charbonnel et al., *Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Added to Ongoing Metformin Therapy in Patients With Type 2 Diabetes Inadequately Controlled with Metformin Alone*, 29 DIABETES CARE 2638–43 (2006) (Ex. 1004).
[2] Hughes, Int'l Pub. No. WO 2005/117861, published December 15, 2005 (Ex. 1005).
[3] Dugi et al., U.S. Patent Publication No. 2007/0281940, published December 6, 2007 (Ex. 1003).

Ground	Basis	References
2	§ 103	Janumet,[4] Nauck,[5] or Ahrén 2008[6] in view of the '940 Publication

In support of its patentability challenge, Petitioner relies on the Declaration of Dr. Mayer B. Davidson. Ex. 1002.

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

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[4] Janumet™ (sitagliptin/metformin HCL) tablets Prescribing Information (Ex. 1007).

[5] Nauck et al., *Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor, Sitagliptin, Compared with the Sulfonylurea, Glipizide, in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone: A Randomized, Double-Blind, Non-Inferiority Trial*, 9 DIABETES, OBESITY AND METABOLISM 194–205 (2007) (Ex. 1006).

[6] Ahrén, Novel Combination Treatment of Type 2 Diabetes DPP-4 Inhibition + Metformin, 4 VASCULAR HEALTH AND RISK MANAGEMENT 383–94 (2008) (Ex. 1022).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any term expressly.

Grounds 1 and 2

For Ground 1, Petitioner argues that claims 1–4 would have been obvious over Charbonnel or Hughes in view of the '940 Publication. Pet. 16–25. For Ground 2, Petitioner argues that claims 1–4 would have been obvious over Janumet, Nauck, or Ahrén 2008 in view of the '940 Publication. Pet. 26–35. Patent Owner contends that Petitioner has not shown that Janumet is a printed publication as defined under 35 U.S.C. § 102(b). Prelim. Resp. 9–13. For purposes of this Decision, we do not need to resolve this issue. Because Petitioner presents the arguments under Ground 2 in the alternative—obviousness over Janumet, Nauck, *or* Ahrén 2008 in view of the '940 Publication, we do not consider Janumet in our analysis.

Patent Owner counters that Petitioner has failed to show a reason for an ordinary artisan to combine the teachings of the asserted prior art and a reasonable expectation of success in combining and modifying the prior-art teachings to arrive at the claimed invention. Prelim. Resp. 13–27.

Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in showing that claims 1–4 would have been obvious over Charbonnel or Hughes in view of the '940 Publication, and over Nauck or Ahrén 2008 in view of the '940 Publication.

Petitioner refers to Charbonnel and Nauck for teaching that sitagliptin, a DPP-4 inhibitor, was effective in treating type II diabetes when added to ongoing metformin therapy for patients with inadequate glycemic control with metformin alone. Pet. 22 (citing Ex. 1004, 2638, 2642–43), 31 (citing Ex. 1006, 201–03). Similarly, Petitioner refers to Hughes for teaching that LAF237, another DPP-4 inhibitor, also known as vildagliptin, was effective in treating type II diabetes when added to ongoing metformin therapy for patients with inadequate glycemic control with metformin alone. *Id.* at 22 (citing Ex. 1005, 2–3, 13). In addition, Petitioner points to Ahrén 2008 for teaching that either sitagliptin or vildagliptin is effective in treating type II diabetes both as add-on therapy to metformin and as initial combination therapy with metformin. *Id.* at 31–32 (citing Ex. 1022, 385–90).

Petitioner relies on the '940 Publication for teaching a method of treating type II diabetes by administering a DPP-4 inhibitor, including linagliptin, and metformin. *Id.* at 22 (citing Ex. 1003 ¶¶ 25, 31, 32, 46), 32 (citing Ex. 1003 ¶¶ 25, 31, 32, 44, 46, 60, 61, 68, and 91). According to Petitioner, linagliptin is listed as "particularly preferred" in the '940 Publication and having "unexpected therapeutic advantages and improvement" when combined with other pharmaceuticals, including metformin. *Id.* at 22, 32. Furthermore, Petitioner contends that the '940 Publication teaches orally administering a DPP-4 inhibitor, such as ligagliptin, in the amount of 5 mg, as recited in claims 1 and 2. *Id.* at 23 (citing Ex. 1003 ¶ 88), 32 (citing Ex. 1003 ¶ 88).

According to Petitioner, an ordinary artisan would have had a reason to substitute the DPP-4 inhibitor sitagliptin or vildagliptin with linagliptin,

"a longer-lasting and particularly preferred" DPP-4 inhibitor, in combination with or as an add-on to metformin treatment to treat a diabetic patient, who is unable to maintain adequate glycemic control with metformin treatment alone. *Id.* at 23–24, 33. In addition, Petitioner asserts that there would have been a reasonable expectation of success in administering 5 mg linagliptin in combination with or as an add-on to metformin to treat a diabetic patient, who is unable to maintain adequate glycemic control with metformin treatment alone. *Id.* at 24, 33–34. As a result, Petitioner concludes that claims 1 and 2 would have been obvious over Charbonnel or Hughes in view of the '940 Publication, or over Nauck or Ahrén 2008 in view of the '940 Publication.

Claims 3 and 4 depend from claim 1 and recite administering linagliptin in the amount of 5 mg once daily and 2.5 mg twice daily, respectively. According to Petitioner, the '940 Publication teaches these additional limitations. Pet. 25, 34–35. Petitioner further argues that "optimizing the dosing amount and frequency of dosing would have been a matter of routine experimentation." *Id.* at 25, 35. Thus, Petitioner contends that claims 3 and 4 are also unpatentable.

At this stage of the proceeding, we find Petitioner's argument and evidence sufficient to satisfy the reasonable likelihood standard of 35 U.S.C. § 314(a). It is undisputed that at the time of the '695 invention, an ordinary artisan recognized the limitations of metformin monotherapy in maintaining glycemic control in diabetic patients. *See, e.g.*, Ex. 1004, 2638; Ex. 1005, 2–3; Ex. 1006, 195; Ex. 1022, 384. An ordinary artisan also recognized that because DPP-4 inhibitors and metformin "target potentially complementary

pathways, the addition of [a DPP-4 inhibitor] for patients with type 2 diabetes who do not have adequate glycemic control with metformin monotherapy may provide improved glycemic control." Ex. 1004, 2638. Indeed, it was known that

> metformin acts primarily by reducing hepatic glucose output and improving insulin sensitivity in liver and muscle[,] whereas DPP-4 inhibitors act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion. The two strategies therefore have the potential to improve different mechanisms, which are defective in type 2 diabetes and therefore an additive or synergistic action when used in combination is anticipated.

Ex. 1022, 385 (citations omitted). Each of Charbonnel, Hughes, Nauck and Ahrén 2008 teaches treating diabetic patients with a DPP-4 inhibitor in combination with or as add-on to metformin when metformin alone provides inadequate glycemic control. Ex. 1004, 2638; Ex. 1005, 2–3, 13; Ex. 1006, 203; Ex. 1022, 383.

The '940 Publication also teaches using DPP-4 inhibitors in conjunction with other antidiabetic agents, including metformin. Ex. 1003 ¶¶ 60, 61, 91. It specifically identifies linagliptin as one of 12 "particularly preferred" DPP-4 inhibitors. *Id.* ¶¶ 31, 32. According to the '940 Publication, these DPP-4 inhibitors, including linagliptin, "are distinguished from structurally comparable DPP-4 inhibitors, as they combine exceptional potency and a long-lasting effect with favourable pharmacological properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances," including metformin. *Id.* ¶ 44.

Patent Owner presents several arguments. For example, according to Patent Owner, the structure of linagliptin is "unrelated and distinct from" those of sitagliptin or vildagliptin. Prelim. Resp. 20. As a result, Patent Owner contends there would have been "substantial uncertainty as to whether these prior art compounds and linagliptin would behave similarly in combination therapy." *Id.* This is merely attorney argument unsupported by persuasive evidence at this stage of the proceeding.

Patent Owner does not dispute Petitioner's assertion that "linagliptin has the same mechanism of action as vildagliptin and sitagliptin." Pet. 24 (citing Ex. 1002 ¶ 57), 34 (citing Ex. 1002 ¶ 79). Thus, based on the current record, we are persuaded that an ordinary artisan, at the time of the '695 patent invention, would have had a reason to substitute sitagliptin or vildagliptin with linagliptin, in combination with or as an add-on to metformin treatment to treat a diabetic patient, who is unable to maintain adequate glycemic control with metformin treatment alone. *See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354–55 (Fed. Cir. 2013).

We are also persuaded that the prior art teaches the orally administered 5 mg per day dosage for linagliptin. The '940 Publication teaches administering the exemplified DPP-4 inhibitors orally in the amount of "0.5 mg to 100 mg, preferably 2.5 mg to 50 mg, in each case 1 to 4 times a day." Ex. 1003, ¶ 46. Specifically, Example 11 teaches tablets comprising DPP-4 inhibitor in oral dosage forms of 0.500 mg, 1.000 mg, 2.500 mg, 5.000 mg, and 10.000 mg. *Id.* ¶ 88. More specifically, Petitioner refers to

Exhibit 1020[7] for "disclosing 5 mg as an effective dose" of linagliptin. Pet. 15 (citing Ex. 1020). The Dugi Reference, coauthored by the inventor of the '695 patent, reports a Phase I clinical study for orally administered linagliptin. Ex. 1020. It concludes that linagliptin "has a wide therapeutic window of >100-fold based on a therapeutic dose of 5 mg," and that "[t]he pharmacokinetic profile is consistent with a once daily dosing regimen." *Id.* Thus, we determine that, at this stage of the proceeding, Petitioner has provided sufficient evidence to show that prior art suggests the recited orally administered linagliptin dosage of 5 mg per day (claim 1), administered in the amount of 5 mg once daily (claim 3), or 2.5 mg twice daily (claim 4).

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–4 of the '695 patent.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted on the following grounds:

1. claims 1–4 as obvious over Charbonnel or Hughes in view of the '940 Publication;

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[7] Dugi et al., *Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BI 1356, a Novel DPP-IV Inhibitor with a Wide Therapeutic Window*, DIABETIC MEDICINE P821 (2006) (Ex. 1020, "the Dugi Reference").

2. claims 1–4 as obvious over Nauck or Ahrén 2008 in view of the '940 Publication;

FURTHER ORDERED that no other ground of unpatentability is authorized in this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '270 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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