UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.
Petitioner

v.

CORCEPT THERAPEUTICS, INC.
Patent Owner

PGR2019-00048
Patent 10,195,214 B2

SECOND DECLARATION OF DR. DAVID J. GREENBLATT, M.D.

I, David J. Greenblatt, M.D., hereby declare as follows:

1. I am over the age of eighteen (18) and competent to make this declaration.

2. I have been retained as an expert witness on behalf of Teva Pharmaceuticals USA, Inc. for the above-captioned post-grant review (PGR). I am being compensated for my time in connection with this PGR at my standard consulting rate, which is $300 per hour, or $3000/day for work requiring out-of-state travel.

3. I understand that this Declaration accompanies a reply in support of Teva's petition for PGR involving U.S. Patent No. 10,195,214 ("the '214 patent") (TEVA1001). I also submitted a Declaration accompanying Teva's petition in May 2019. In that Declaration, I discussed my background and qualifications to offer expert opinions in this matter. My CV (TEVA1003) provides further information about my background and qualifications. In short, I am an expert in clinical pharmacology, pharmacokinetics, drug metabolism, and drug interactions—particularly those involving CYP3A inhibitors—and have been since prior to March 1, 2017.

4. I understand that Corcept has proposed a definition for a person of ordinary skill in the art ("POSA") that differs from my proposed definition in that, in Corcept's view, the POSA or team making up the POSA also requires a medical

professional with experience treating Cushing's syndrome. I disagree with Corcept's proposed definition and maintain that the definition set forth in my initial declaration is correct. TEVA1002, ¶18. However, the opinions set forth in my initial declaration and in this second declaration would be the same regardless of which definition is applied. I note that even under Corcept's definition of a POSA I would still be an integral part of the "team" making up the POSA in view of my extensive knowledge and experience with clinical studies of drug-drug interactions involving CYP3A inhibitors.

5. Counsel for Teva asked me to review and respond to certain opinions set forth in the declaration of Dr. F. Peter Guengerich (EX2056). I disagree with several of those opinions for reasons explained below. My failure to comment on a specific opinion of Dr. Guengerich's should not be interpreted as an agreement with that opinion.

6. In formulating my opinions in this case, I have considered all the references and documents cited in this declaration and my first declaration, including those listed below.

Exhibit #	***Description***
1001	Belanoff, J.K., "Concomitant Administration Of Glucocorticoid Receptor Modulators And CYP3A Inhibitors," U.S. Patent No. 10,195,214 B2 (filed June 19, 2017; issued February 5, 2019)
1003	Curriculum Vitae for David J. Greenblatt. M.D.
1004	Korlym Label (2012)

1005	Lee *et al*., Office of Clinical Pharmacology Review NDA 20687 (Addendum, Korlym™, Mifepristone) (2012)
1006	FDA Approval Letter for Korlym (mifepristone) tablets, NDA 20217, dated February 17, 2012
1007	Tsunoda, S.M., *et al*., "Differentiation of intestinal and hepatic cytochrome P450 3A activity with use of midazolam as an in vivo probe: Effect of ketoconazole," *Clin. Pharmacol. Ther.* 66(5): 461-471 (1999)
1015	Sitruk-Ware, R. and Spitz, I.M., "Pharmacological properties of mifepristone: toxicology and safety in animal and human studies," *Contraception* 68: 409–420 (2003)
1022	Jang, G.R., *et al*., "Identification of CYP3A4 as the Principal Enzyme Catalyzing Mifepristone (RU 486) Oxidation in Human Liver Microsomes," *Biochem. Pharmacol.* 52: 753-761 (1996)
1023	Greenblatt, D., "*In Vitro* Prediction of Clinical Drug Interactions With CYP3A Substrates: We Are Not There Yet," *Clin. Pharm. Ther*. 95(2): 133-135 (2014)
1024	Greenblatt, D.J., *et al*., "Mechanism of cytochrome P450-3A inhibition by ketoconazole," *J. Pharm. Pharmacol.* 63: 214–221 (2011)
1025	Greenblatt, D.J. and von Moltke, L.L., "Clinical Studies of Drug-Drug Interactions: Design and Interpretation," in *Enzyme- and Transporter-Based Drug-Drug Interactions: Progress and Future Challenges*. Pang, K.S. *et al*., ed., pp. 625-649, New York, Springer: (2010)
1026	Greenblatt, D.J., *et al*., "The CYP3 Family" in *Cytochromes P450: Role in the Metabolism and Toxicity of Drugs and other Xenobiotics*. Ionnides, C., ed., pp. 354-383, Royal Society of Chemistry: (2008)
1027	Ohno, Y., *et al*., "General Framework for the Quantitative Prediction of CYP3A4-Mediated Oral Drug Interactions Based on the AUC Increase by Coadministration of Standard Drugs," *Clin. Pharmacokinet.* 46(8): 681-696 (2007)
1034	Nguyen, D. and Minze, S., "Effects of Ketoconazole on the Pharmacokinetics of Mifepristone, a Competitive Glucocorticoid

	Receptor Antagonist, in Healthy Men," *Adv. Ther.* 34:2371–2385 (2017)
1035	File History of U.S. Patent No. 10,195,214 B2
1037	Kaesar, B., *et al*., "Drug-Drug Interaction Study of Ketoconazole and Ritonavir-Boosted Saquinavir," *Antimicrobial Agents and Chemotherapy* 53(2): 609–614 (2009)
1040	"A Guide to Drug Safety Terms," FDA Consumer Health Information / U. S. Food and Drug Administration, (2012) downloaded from www.tinyurl.com/y6oao2sj
1041	"Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER)., Center for Biologics Evaluation and Research (CBER) (2006)
1046	Greenblatt, D.J, *et al*., "Ketoconazole inhibition of triazolam and alprazolam clearance: Differential kinetic and dynamic consequences," *Clin. Pharmacol. Ther*. 64(3):237-247 (1998)
1057	Greenblatt, D.J. and Koch-Weser, J., "Clinical Pharmacokinetics," *NEJM* 293:702-705 (1975)
1058	Greenblatt, D.J. and Abourjaily, P.N., "Pharmacokinetics and Pharmacodynamics for Medical Students:A Proposed Course Outline," *J. Clin. Pharmacol.* 56(10): 1180–1195 (2016)
1059	Friedman, H. and Greenblatt, D.J., "Rational Therapeutic Drug Monitoring," *JAMA* 256(16): 2227–2233 (1986)
1066	Weber, J.M, *et al.*, Other Review(s) NDA 202107 (Korlym™, Mifepristone) (2012) [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000OtherR.pdf]
1073	Banankhah, P.A., *et al.,* "Ketoconazole-Associated Liver Injury in Drug-Drug Interaction Studies in Healthy Volunteers," *Journal of Clinical Pharmacology* 56(10):1196–1202 (2016)
1074	Outeiro, N., *et al.*, "No Increased Risk of Ketoconazole Toxicity in Drug-Drug Interaction Studies," *J. Clin. Pharmacol.* 56(10):1203–1211 (2016)
1080	Locniskar, A., *et al.*, "Interaction of diazepam with famotidine and cimetidine, two H2-receptor antagonsits," *J. Clin. Pharmacol.* 26(4):299–303 (1986)

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