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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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TABLE OF CONTENTS

I.	Intro	duction	1
II.	Corcept's arguments regarding the definition of a POSA betray a misunderstanding of the obviousness inquiry.		
III.		OSA would have arrived at the claimed 600-mg dose through ne optimization	8
	A.	A POSA would have reasonably expected success in optimizing the dose by conducting a drug-drug interaction study	8
	В.	Corcept's contrary arguments lack merit. 1. FDA recommended permitting co-administration of strong CYP3A inhibitors and 300 mg mifepristone and contemplated increasing the permitted dose pending the results of the DDI study. 2. Dunnigan would not have led a POSA to expect that co-administering strong CYP3A inhibitors with 600 mg mifepristone would be dangerous. 3. The unpredictability of the DDI simply reinforces the motivation to perform a clinical DDI study.	17
IV.	the e	cept's suggestion that obviousness requires the ability to predict exact dosing without experimentation is legally incorrect	
V	Cond	clusion	76



LIST OF EXHIBITS

Teva 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)
1002	Declaration of David J. Greenblatt, M.D.
1003	Curriculum Vitae for David J. Greenblatt. M.D.
1004	Korlym Label (2012)
1005	Lee <i>et al.</i> , Office of Clinical Pharmacology Review NDA 20687 (Addendum, Korlym TM , Mifepristone) (2012)
1006	FDA Approval Letter for Korlym (mifepristone) tablets, NDA 20217, dated February 17, 2012
1007	Tsunoda, S.M., <i>et al.</i> , "Differentiation of intestinal and hepatic cytochrome P450 3A activity with use of midazolam as an in vivo probe: Effect of ketoconazole," <i>Clin. Pharmacol. Ther.</i> 66(5): 461–471 (1999)
1008	Ullmann, A., et al., "Method For Treating Cushing's Syndrome," U.S. Patent Application Publication No. 2010/0261693 A1 (filed October 13, 2008; published October 14, 2010)
1009	Sartor, O. and Cutler, G.B., "Mifepristone: Treatment of Cushing's Syndrome," <i>Clinical Obstetrics and Gynecology</i> 39(2): 506–510 (1996)
1010	Pozza, C., <i>et al.</i> , "Management Strategies for Aggressive Cushing's Syndrome: From Macroadenomas to Ectopics," <i>J. Oncol.</i> 109: 1–9 (2012)
1011	Castinetti, F., "Medical Treatment of Cushing's Syndrome: Glucocorticoid Receptor Antagonists and Mifepristone," Neuroendocrinology 92(suppl. 1): 125–130 (2010)
1012	Nieman, L.K., "Successful Treatment of Cushing's Syndrome with the Glucocorticoid Antagonist RU 486*," <i>J. Clin. Endocrinol. Metab.</i> 61(3): 536–540 (1985)



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1013	Brogden, R.N., <i>et al.</i> , "Mifepristone A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential," <i>Drugs</i> 45(3): 384–409 (1993)
1014	Molitch. M.E., "Current approaches to the pharmacological management of Cushing's disease," <i>Mol. Cell. Endocrinol.</i> 408: 185–189 (2015)
1015	Sitruk-Ware, R. and Spitz, I.M., "Pharmacological properties of mifepristone: toxicology and safety in animal and human studies," <i>Contraception</i> 68: 409–420 (2003)
1016	Heikinheimo, O., "Pharmacokinetics of The Antiprogesterone RU 486 in Women During Multiple Dose Administration," <i>J. Steriod. Biochem.</i> 32(1A): 21–25 (1989)
1017	Heikinheimo, O., <i>et al.</i> , "The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action," <i>Contraception</i> 68: 421–426 (2003)
1018	Blasey, C.M., <i>et al.</i> , "Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression," <i>J. Clin. Psychopharmacol.</i> 31:436–440 (2011)
1019	Belanoff, J.K., "Optimizing Mifepristone Levels in Plasma Serum of Patients Suffering from Mental Disorders Treatable with Glucocorticoid Receptor Antagonists," U.S. Patent No. 8,921,348 B2 (filed October 29, 2013; issued December 30, 2014)
1020	Belanoff, J.K., "Optimizing Mifepristone Levels in Plasma Serum of Patients Suffering from Mental Disorders Treatable with Glucocorticod Receptor Antagonists," U.S. Patent No. 8.598,149 B2 (filed August 27, 2008; issued December 3, 2013)
1021	Castinetti, F., et al., "Merits and pitfalls of mifepristone in Cushing's syndrome," Eur. J. Endocrinol. 160: 1003–1010 (2009)
1022	Jang, G.R., <i>et al.</i> , "Identification of CYP3A4 as the Principal Enzyme Catalyzing Mifepristone (RU 486) Oxidation in Human Liver Microsomes," <i>Biochem. Pharmacol.</i> 52: 753–761 (1996)



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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," <i>J. Pharm. Pharmacol.</i> 63: 214–221 (2011)
1025	Greenblatt, D.J. and von Moltke, L.L., "Clinical Studies of Drug- Drug Interactions: Design and Interpretation," in <i>Enzyme- and</i> <i>Transporter-Based Drug-Drug Interactions: Progress and Future</i> <i>Challenges</i> . Pang, K.S. <i>et al.</i> , 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)
1028	Archive History of NCT00936741 History of Changes for Study: NCT00936741 An Extension Study of CORLUX in the Treatment of Endogenous Cushing's Syndrome (July 9, 2009) on ClinicalTrials.gov
1029	Fleseriu, M., <i>et al.</i> , "Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome," <i>J. Clin. Endocrinol. Metab.</i> 97(6):2039–2049 (2012)
1030	Morgan, F.H. and Laufgraben, M.J., "Mifepristone for Management of Cushing's Syndrome," <i>Pharmacotherapy</i> 33(3):319–329 (2013)
1031	Schteingart, D.E., "Drugs in the medical treatment of Cushing's syndrome," <i>Expert Opin. Emerging Drugs</i> 14(4):661–671 (2009)



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