UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC. and MYLAN LABORATORIES LIMITED,
Petitioners,

v.

UCB PHARMA GMBH,
Patent Owner.

Case Nos. IPR2016-00510; IPR2016-00512; IPR2016-00514; IPR2016-00516; IPR2016-00517
Patent Nos. 6,858,650; 7,384,980; 7,855,230; 8,338,478; 7,985,772

DECLARATION OF SCOTT A. MACDIARMID, M.D., FRCPSC

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I. INTRODUCTION

1. I, Scott A. MacDiarmid, M.D., FRCPSC, have been retained by White & Case LLP, counsel for Patent Owner UCB Pharma GmbH ("UCB"), as an expert witness in the above-captioned *inter partes* review of United States Patent Nos. 7,384,980 (the "'980 patent"), 7,855,230 (the "'230 patent"), 8,338,478 (the "'478 patent"), and 7,985,772 (the "'772 patent") (collectively, the "'980 patent family") and 6,858,650 (the "'650 patent"). I understand that Mylan Pharmaceuticals Inc. and Mylan Laboratories Limited (collectively with Mylan Pharmaceuticals Inc., "Petitioner") have petitioned for *inter partes* review of the '980 patent family and the '650 patent, and request that the United States Patent and Trademark Office ("PTO") cancel as unpatentable certain claims of the '980 patent family and the '650 patent.

2. This declaration sets forth my analyses and opinions based on the materials I have considered thus far, as well as the bases for my opinions. I understand that this declaration will be used in each of the above-mentioned petitions, as the subject matter is overlapping.

A. Background and Qualifications

3. I have practiced as a urologist since I was certified as a Fellow of the Royal College of Physicians and Surgeons of Canada ("FRCPSC") in September 1991. After relocating to the United States, I was certified by the American Board

of Urology in February 1996 and have been practicing in the United States since that time.

4. Presently, I am the Director of the Alliance Urology Specialists Bladder Control and Pelvic Pain Center in Greensboro, North Carolina and a Clinical Associate Professor in the Department of Urology at the University of North Carolina at Chapel Hill. I am a sub-specialist in Reconstructive Urology and urinary incontinence and have over 20 years of experience in treating male and female patients with voiding dysfunction and overactive bladder. I have been affiliated with the Moses Cone Health System in Greensboro, North Carolina since 2006. I previously held university appointments at Wake Forest University School of Medicine, the University of Tennessee, and the University of Arkansas for Medical Sciences. I was also previously an attending urologist at North Carolina Baptist Hospitals, Inc. in Winston-Salem, North Carolina.

5. I received my B.S. and M.D. from Dalhousie University in Halifax, Nova Scotia in 1981 and 1985, respectively. For my clinical training, I was a rotating intern at Dalhousie University in 1985-1986 and a resident in urology at Dalhousie University in 1987-1991. Between 1991 and 1993, I completed fellowships in Reconstructive Urology and Urodynamics at Duke University Medical Center, in Reconstructive Urology and Urodynamics at the University of Otago in

Christchurch, New Zealand, and in Neuro-Urology and Reconstructive Urology at the Lodgemoor Spinal Unit of the University of Sheffield in England.

6. I am presently a reviewer for numerous peer-reviewed journals, including the Journal of Urology, Urology, World Journal of Urology, International Urogynecology Journal, Neurology and Urodynamics, and the International Journal of Clinical Practice.

7. I have been a Visiting Professor or Guest Lecturer at numerous university or industry conferences. I have acted as a primary investigator or co-investigator on numerous clinical trials, including trials related to fesoterodine, tolterodine, oxybutynin, mirabegron, and solifenacin. I have served as a key opinion leader and/or served on advisory boards for numerous pharmaceutical companies in connection with their overactive bladder ("OAB") treatments, including Ortho-McNeil, Pfizer, Astellas, Watson, Novartis, Schwarz, GlaxoSmithKline, Allergan, and Sanofi-Aventis. I have published numerous articles in peer-reviewed literature, many focusing on the management of patients with OAB.

8. A copy of my *curriculum vitae*, which sets forth additional information regarding my education and experience, is attached as Exhibit 2060.

B. Materials Considered

9. The opinions that I express in this declaration are based on the information and evidence currently available to me. The following table lists the

materials that I considered in forming my opinions set forth in this declaration. I also relied on my extensive knowledge of the OAB literature, experience, and my understandings based on my interactions with urologists and other physicians.

Exhibit No.	Materials
1001	The United States Patent that is the subject of this proceeding (either U.S.P.N. 7,384,980; 7,855,230; 8,338,478; 7,985,772; or 6,858,650).
1002	The file history for Exhibit 1001.
1003	Declaration of Dr. Steven Patterson, Ph.D.
1004	C.V. for Dr. Steven Patterson, Ph.D.
1005	WO 94/11337 Filed 6 November 1992 – "Novel 3,3-Diphenylpropylamines, Their Use and Preparation" ("Johansson").
1006	BJU International (1999), 84, 923-947 – "The Pharmacological Treatment of Urinary Incontinence"; KE Andersson, R. Appell, L.D. Cardozo, C. Chapple, H.P. Drutz, A.E. Finkbeiner, F. Haab, and R. Vela Navarrete ("Andersson Review").
1007	N. Brynne et al., Pharmacokinetics and Pharmacodynamics of Tolterodine in Man: A New Drug for the Treatment of Urinary Bladder Overactivity, 35 INT'L J. CLIN. PHARMACOLOGY & THERAPEUTICS 287 (1997) ("Brynne 1997").
1008	British Heart Journal (1995), 74, 53-56 – "Concentration dependent cardiotoxicity of terodine in patients treated for urinary incontinence"; S. Thomas, P. Higham, K Hartigan-Go, F. Kamali, P. Wood, R. Campbell, and G. Ford ("Thomas").
1009	Detrol® Label.
1010	Drug Metabolism and Disposition (1998), 26 (4), 289-293 – "Tolterodine, A New Muscarinic Receptor Antagonist, Is Metabolized by Cytochromes P450 2D6 and 3A in Human Liver Microsomes"; H. Postlind, A. Danielson, A. Lindgren, and S. Andersson ("Postlind").
1011	Niclas Brynne et al., Influence of CYP2D6 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Tolterodine, 63 CLIN. PHARMACOLOGY & THERAPEUTICS 529 (1998) ("Brynne 1998").

1012	Hans Bundgaard, DESIGN OF PRODRUGS (Hans Bundgaard ed. 1985) ("Bundgaard").
1013	JOURNAL OF PHARMACEUTICAL SCIENCES (1977), 66 (1), 1-19 – "*Pharmaceutical Salts*"; S. Berge, L., Bighley, and D. Monkhouse ("Berge").
1014	Drug Metabolism and Disposition (1998), 26(6), 528-535 – "*Biotransformation of tolterodine, a new muscarinic receptor antagonist, in mice, rats, and dogs*"; S. Andersson, A. Lindgren, and H. Postlind ("Andersson 1998").
1015	Lisbeth Nilvebrant et al., *Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine*, 81 PHARMACOLOGY & TOXICOLOGY 169 (1997) ("Nilvebrant 1997").
1016	P&T (2012), 37(6), 345-361 – "*Management of Urinary Incontinence*"; G. DeMaagd and T. Davenport ("DeMaagd").
1017	UROLOGY (1997), 50, 90-96 – "*Clinical efficacy and safety of tolterodine in the treatment of overactive balder: a pooled analysis*"; R. Appell ("Appell").
1018	Home Care Provider (1997), 2(3), 117-120 – *Is My Antihistamine Safe?,* L. Ashworth ("Ashworth").
1019	Christopher A. Lipinski et al., *Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings,* Advanced Drug Delivery Reviews 23 (1997) 3-25 ("Lipinski").
1020	WO 92/08459 Filed 11 November 1991 – "Topical Compositions for Transdermal Delivery of Prodrug Derivatives of Morphine" ("Bundgaard patent").
1021	American Urological Association Education and Research (2014) – "Diagnosis and Treatment of Overactive Bladder (Non-Neorogenic) in Adults: AUA/SUFU Guideline"; E. Gormley, et al. ("AUA Guideline").
1022	Aug. 2, 2012 "Study Shows Toviaz is Effective in Reducing Urge Urinary Incontinence in Patients with Overactive Bladder After Suboptimal Response to Detrol LA" – www.pfizer.com ("Pfizer 2012 Press Release").

1023	April 1, 2012 "Overactive Bladder Market: Managing the Future" – www. pm360online.com ("PM360").
1024	"Toviaz® Label" – Pfizer Labs.
1025	"FDA Approval Letter" –NDA20-771.
1026	Applications Covered by Section 505(b)(2) – October 1999 – FDA (CDER) ("FDA Guidance").
1027	INTERNATIONAL JOURNAL OF PHARMACEUTICS (1986), 3, 201-217 – "*Salt Section for Basic Drugs*"; P. Gould ("Gould").
1028	Discovery & Development of Selective M3 Antagonists for Clinical Use, 60 LIFE SCIENCE 1053 (1997) ("Alabaster").
1029	1,2,3,4-Tetrahydro-2-Isoquinolinecarboxylate Derivatives: A Novel Class of Selective Muscarinic Antagonists, III, in 213th ACS National Meeting, San Francisco, Abst. 046 (Apr. 13-17, 1997) ("Takeuchi").
1030	CLINICAL PHARMACOLOGY & THERAPEUTICS (1997) 61(1), 59-69 – "*DuP 532, an angiotensin II receptor antagonist: First Administration and comparison with losartan*"; M. Goldberg, M. Lo, D. Christ, R. Chiou, C. Furtek, O. Amit, A. Carides, J. Biollaz, V. Piguet, J. Nussberger, H. Brunner ("Goldberg").
1031	J. PHARM. PHARMACOL. (1996), 48, 136-146 – "*The Blood-brain Barrier: Principles for Targeting Peptides and Drugs to the Central Nervous System*"; D. Begley ("Begley").
2001	Memorandum Opinion, *Pfizer Inc. et al. v. Sandoz, Inc. et al*, 13-cv-01110 (D. Del.).
2004	Lisbeth Nilvebrant, *Tolterodine: A New Bladder-Selective Muscarinic Receptor Antagonist*, LIFE SCIENCES 60:1129-37 (1997).
2005	Ernesto Callegari et al., *A Comprehensive Non-Clinical Evaluation of the CNS Penetration Potential of Antimuscarinic Agents For the Treatment of Overactive Bladder*, BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 72:2, 235-46 (2011).
2006	Trial Transcript, July 13-16, 2015, *Pfizer Inc. et al. v. Sandoz, Inc. et al*, 13-cv-01110 (D. Del.).
2007	The file history of United States Patent No. 7,384,980.
2018	United States Patent No. 7,384,980.

2020	Transcript of the Deposition of Steven Patterson, Ph.D., dated October 4, 2016, Case IPR2016-00510, Case IPR2016-00512, Case IPR2016-00514, Case IPR2016-00516, Case IPR2016-00517 ("Patterson Tr.").
2024	Declaration of Leonard J. Chyall, Ph.D., *Mylan Pharms. Inc. and Mylan Labs. Ltd. v. UCB Pharma GmbH*, Case IPR2016-00510, Case IPR2016-00512, Case IPR2016-00514, Case IPR2016-00516, Case IPR2016-00517.
2026	Transcript of the Deposition of Culley C. Carson, III, M.D., dated August 25, 2016, C.A. No. 15-cv-0079 ("Carson Tr.").
2032	Lisbeth Nilvebrant et al., *Tolterodine – A New Bladder-Selective Antimuscarinic Agent*, EUROPEAN JOURNAL OF PHARMACOLOGY 327 (1997) (Nilvebrant II (1997)).
2040	Lisbeth Nilvebrant, Clinical Experiences with Tolterodine, 68 Life. Sci. 2549 (2001) ("Nilvebrant 2001").
2060	C.V. of Scott A. MacDiarmid.
2061	Paul Abrams et al., *The Standardisation of Terminology of Lower Urinary Tract Function*, NEUROUROL. URO. 21:167–78 (2002).
2062	Abrams P, Cardozo L, Khoury S, Wein A (eds), *Incontinence*, 5th International Consultation on Incontinence (5th Ed. 2013).
2063	Paul Abrams et al., *Overactive Bladder Significantly Affects Quality of Life*, AMERICAN JOURNAL OF MANAGED CARE 6:11, S580-S590 (2000).
2064	Walter F. Stewart et al., *The prevalence and impact of overactive bladder in the U.S.: results from the NOBLE program,* Neurourol Urodyn. at 406-8 (2001).
2065	Christopher Chapple & Lisbeth Nilvebrant, *Tolterodine: Selectivity for the Urinary Bladder Over the Eye (as Measured by Visual Accommodation) in Healthy Volunteers*, DRUGS R&D 3(2): 75-81 (2002).
2066	Christopher Chapple, et al., *The Effects of Antimuscarinic Treatments in Overactive Bladder: An Update of a Systematic Review and Meta-Analysis*, EUROPEAN UROLOGY 54 at 558-559 (2008).
2067	FDA, *Drugs@FDA:Ditropan*, https://www.accessdata.fda.gov/scripts/cder/drugsatfda/ index.cfm (last visited Oct. 14, 2016).

2068	Karl-Erik Andersson, *Current Concepts in the Treatment of Disorders of Micturition*, DRUGS 35:477-494, 481 (1988).
2069	M.M.S. Stahl, *Urodynamic and Other Effects of Tolterodine: a Novel Antimuscarinic Drug for the Treatment of Detrusor Overactivity*, NEUROUROL. URO. 14: 647-655 (1995).
2070	Detrol® LA Prescribing Information, Revised 08/2012.
2071	Bimal Malhotra et al. *Thorough QT Study with Recommended and Supratherapeutic Doses of Tolterodine*, CLINICAL PHARMACOLOGY & THERAPEUTICS 81:377-385 (2007).
2072	NDA 20-771 Approval Package.
2073	Martin C. Michel, *Fesoterodine: A Novel Muscarinic Receptor Antagonist for the Treatment of Overactive Bladder Syndrome*, EXPERT OPIN. PHARMACOTHER. 9: 1787-96 (2008).
2074	Bimal Malhotra, et al., *The Design and Development of Fesoterodine as a Prodrug of 5-Hydroxymethyl Tolterodine (5-HMT), the Active Metabolite of Tolterodine*, CURRENT MEDICINAL CHEMISTRY, 16:33, 4481-89 (2009).
2075	Victor Nitti, et al., *Fesoterodine is an Effective Antimuscarinic for Patients with Overactive Bladder (OAB): Results of a Phase 2 Trial.*
2076	Christopher Chapple, *Fesoterodine, a New Effective and Well-Tolerated Antimuscarinic for the Treatment of Urgency-Frequency Syndrome: Results of a Phase 2 Controlled Study*, NEUROUROL. URODYN., 23 (5-6) (2004) (hereinafter, "Chapple (2004).
2077	Chapple C, Van Kerrebroeck P, Tubaro A, et al. *Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder.* EUR UROL. 52(4):1204-1212 (2007).
2078	Nitti VW, Dmochowski R, Sand PK, et al. *Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome.* J UROL. 178(6):2488-2494 (2007).
2079	Dmochowski RR, Peters KM, Morrow JD, et al. *Randomized, double-blind, placebo-controlled study of flexible-dose fesoterodine in subjects with overactive bladder.* UROLOGY. 75(1):62-68 (2010).

2080	Sender Herschorn et al., *Efficacy and Tolerability of Fesoterodine in Men With Overactive Bladder: A Pooled Analysis of 2 Phase III Studies*, J. UROLOGY. 75 (5), 1149-1155 (2010).
2081	Vik Khullar, et al., *Fesoterodine Dose Response in Subjects with Overactive Bladder Syndrome*, FEMALE UROLOGY (2008).
2082	Steve Chaplin and Adrian Wagg, *Fesoterodine (Toviaz): New Option for Overactive Bladder*, PRESCRIBER 5, *available at* www.prescriber.co.uk (Table 2) (2008).
2083	Bimal Malhotra, et al., *Thorough QT Study of the Effect of Fesoterodine on Cardiac Repolarization*, INT'L J. PHARMACOLOGY & THERAPEUTICS, 48:309-18 (2010).
2084	Gary Kay et al., *Evaluation of Cognitive Function in Healthy Older Subjects Treated with Fesoterodine*, POSTGRADUATE MEDICINE, Volume 124, Issue 3, 7-15 (May 2012).
2085	Chapple, C. et al., *Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial*, BRIT. J. UROLOGY INT'L. 114:418-426 (2014).
2086	Wyndaele, J.J. et al., *Flexible dosing with fesoterodine 4 and 8 mg: a systematic review of data from clinical trials*, Int'l J. Clin. Prac. 68:7, 830-840 (2014).
2087	Sender Herschorn, et al., *Comparison of Fesoterodine and Tolterodine Extended Release for the Treatment of Overactive Bladder: A Head-to-Head Placebo-Controlled Trial*, BJU INT'L, 105:58-66 (2009).
2088	Steven A. Kaplan, et al., *Superior Efficacy of Fesoterodine over Tolterodine Extended Release with Rapid Onset: a Prospective, Head-to-Head Placebo-Controlled Trial*, BRIT. J. URO. 107, 1432-40 (2010).
2089	Christopher Chapple, et al., *Comparison of Fesoterodine and Tolterodine in Patients with Overactive Bladder*, BJU INT'L, 102:1128-32 (2008).
2090	Steven A. Kaplan, et al., *Efficacy and Safety of Fesoterodine 8 mg in Subjects with Overactive Bladder after a Suboptimal Response to Tolterodine ER*, INT'L J. CLIN. PRACTICE 68:9, 1065-1073 (2014).

2091	MacDiarmid, S. *Overactive Bladder: Improving the Efficacy of Anticholinergics by Dose Escalation*, CURRENT UROLOGY REPORTS. 4:446-451 (2003).

II. SUMMARY OF OPINIONS

10. I have reviewed the Declaration of Steven E. Patterson, Ph.D. (the "Patterson Decl."), Petitioner's Petitions for *inter partes* review of U.S. Patent Nos. 7,384,980, 7,855,230, 8,338,478, 7,985,772, and 6,858,650, the specifications, claims, and file histories of the '980 patent family, as well as the '650 patent and its associated file history, and the PTAB's Decision on Institution of the '650 patent. I disagree with a number of the opinions expressed in the Patterson Declaration and the positions taken in the Petition.

11. Based on my experience and expertise, I have been asked to describe and provide background on urinary incontinence and OAB, and the treatment of these conditions. In particular, I have been asked to describe how these conditions are treated with pharmaceuticals, including Toviaz®, both today and historically. A summary of this background is provided below.

12. I have been asked to opine on whether fesoterodine satisfied any previously unmet need. Before the invention of fesoterodine, the primary pharmaceutical treatments for OAB available were oxybutynin and tolterodine in immediate release form. These treatments possessed similar efficacy and differed primarily in terms of tolerability. Fesoterodine satisfied a need for a treatment

with improved efficacy, excellent safety and tolerability, and a superior efficacy/tolerability/safety profile. In practice, fesoterodine met a long-felt unmet need for a treatment that offered "true" dose-escalation in incontinence drug therapy, meaning that fesoterodine's excellent efficacy and favorable efficacy/safety/tolerability profile has been found to be dose-dependent. This breakthrough offered a clinical benefit for the millions of patients that could not, as a clinically practical matter, obtain relief or reach their treatment goal from the treatments available at that time. I am not aware of any prior art[1] that indicated that fesoterodine would satisfy this unmet need.

13. I have been asked to opine on whether fesoterodine possesses any favorable or unexpected results as compared to the previously available OAB treatments. As above, fesoterodine offers a "true" dose-escalation treatment option, superior efficacy and/or an improved efficacy/tolerability/safety profile compared to the other treatments available at the time of its invention. These qualities were unexpected and could not have been predicted based on the prior art, including the prior art that concerns tolterodine and its active metabolite, 5-hydroxymethyl-tolterodine ("5-HMT").

[1] "Prior art" is defined below at ¶ 24.

III. LEGAL STANDARDS

14. I am not an attorney, and therefore, my understanding of patent law and the legal standards set forth in this report is based on explanations provided by counsel.

15. I understand that even if an alleged claimed invention is not identically disclosed or described in a single piece of prior art, the patent claim may still be unpatentable if the differences between the claimed invention and the prior art (alone or in combination) are such that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. I understand that the level of ordinary skill in the pertinent art is evaluated as of the time of the invention, here the priority dates of the '980 patent family and the '650 patent.

16. I also understand that, in addressing obviousness, the following factors must be considered from the perspective of a hypothetical person of ordinary skill in the relevant art: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any other indications ("objective indicia") of non-obviousness, such as commercial success, long-felt but unsolved needs, failure of others, industry acclaim, and unexpected results.

17. I understand that if an experiment leads to unexpected results or a compound exhibits unexpected properties, that result or compound likely would not have been obvious to a person of ordinary skill in the pertinent art. In that instance, such unexpected results or properties suggest that the compound would not have been obvious.

IV. THE CHALLENGED CLAIMS

18. I understand that Petitioner has petitioned for review and cancellation of the following claims (collectively, the "challenged claims"):

- Claims 1-16 of the '980 patent;
- Claims 1-5 of the '230 patent;
- Claims 1-3, 5-8, and 10-12 of the '478 patent;
- Claims 1, 3, 4, and 6-8 of the '772 patent; and
- Claims 1-5 and 21-24 of the '650 patent.

19. I have reviewed the Declaration of Dr. Leonard Chyall and understand that the challenged claims cover the chemical compound fesoterodine, which is the active ingredient in Toviaz®, salt forms of fesoterodine, pharmaceutical compositions containing fesoterodine, or methods of treating overactive bladder ("OAB") with fesoterodine. Declaration of Leonard J. Chyall, Ph.D., *Mylan Pharms. Inc. and Mylan Labs. Ltd. v. UCB Pharma GmbH*, Nos. IPR2016-00510, IPR2016-00512, IPR2016-00514, IPR2016-00516, IPR2016-00517 (Ex. 2024). I

am familiar with the drug Toviaz®, and I am knowledgeable about tolterodine, its metabolite 5-HMT, and fesoterodine.

20. I understand that the dosages of fesoterodine used in Toviaz (4 and 8 mg) are effective dosages, given that they are the FDA-approved dosage strengths for the drug. *See* Ex. 1024 (Toviaz Label). I can also attest from my clinical experience that the dosages of fesoterodine used in Toviaz are effective dosages.

21. I understand that Petitioner alleges that the challenged claims are invalid because fesoterodine and the use of fesoterodine to treat OAB would have been obvious as of the priority date of the '980 patent family and/or the '650 patent.

22. I understand that the priority date of the '980 patent family is May 12, 1998. I understand that the priority date of the '650 patent is November 16, 1999. I note that Dr. Patterson assessed the prior art as of May 11, 1998 in his Declaration. Ex. 1003 (Patterson Decl.) at ¶ 24. Except where expressly stated below, I have conducted my analysis as of that date as well, and I note where my opinion would change if the art were assessed as of November 16, 1999.

23. I also understand that between July 20-26, 2016, the PTAB instituted *inter partes* review of the challenged claims on the following grounds:

- Obviousness over the combination of Postlind (Exhibit 1010), the Bundgaard Publications (Exs. 1012 and 1020), the Detrol® Label (Ex. 1009), and Berge (Ex. 1013); and

- Obviousness over the combination of Brynne 1998 (Ex. 1011), Bundgaard (Ex. 1012), and Johansson (Ex. 1005).

Paper 12 (July 20, 2016) ("'980 Decision") at 29; Paper 12 (July 20, 2016) ("'772 Decision") at 29; Paper 12 (July 20, 2016) ("'650 Decision") at 29; Paper 12 (July 22, 2016) ("'230 Decision") at 29; Paper 12 (July 26, 2016) ("'478 Decision") at 30.

V. PERSON HAVING ORDINARY SKILL IN THE ART

24. I understand that a patent claim is invalid for obviousness if, after consideration of the relevant knowledge that was publicly available as of the claim's priority date (the "prior art"), a "person of ordinary skill in the art" would have found the differences between the prior art and the claimed invention to be obvious. My understanding is that the term "person of ordinary skill in the art" refers to a typical scientist or researcher having average skill in the technical field to which the patented inventions relate.

25. In this case, the patents-in-suit relate to the field of treatment of overactive bladder with pharmaceuticals. As of the relevant dates, a person conducting research in that field would need knowledge of various technical disciplines, including medicinal chemistry, pharmacology, and pharmaceutics, as well as an understanding of the physiology of the bladder and the causes and symptoms of overactive bladder.

26. I have reviewed Petitioner's definition of a person of ordinary skill in the art (Pet. at 6 (citing Ex. 1003 (Patterson Decl.) at ¶¶ 22-23)) and I understand that the PTAB has accepted Petitioner's definition for purposes of institution (Paper 12 (Decision) at 6.). I have applied my definition in forming my opinions. However, my opinions do not change if I apply Petitioner's definition of a person of ordinary skill in the art.

VI. BACKGROUND

A. Overview of Overactive Bladder ("OAB")

27. OAB is a symptom complex defined as urinary urgency with or without urgency incontinence, usually with urinary frequency and nocturia, in the absence of pathologic or metabolic factors that would explain these symptoms. *See, e.g.*, Paul Abrams et al., *The Standardisation of Terminology of Lower Urinary Tract Function*, NEUROUROL. URO. 21:167–78 (2002) (Ex. 2061).

28. OAB is associated with involuntary contractions of the bladder muscle before the bladder is full. These premature contractions may cause one or more of the following symptoms – intense urges to urinate ("urgency"), frequent urination ("frequency"), and/or unintentional leakage from the bladder ("urgency incontinence," formerly known as "urge incontinence"). Patients with one or more of these three symptoms are diagnosed as suffering from OAB. *See, e.g.*, Abrams P, Cardozo L, Khoury S, Wein A (eds), Incontinence, 5th International

Consultation on Incontinence (5th Ed. 2013) (Committee 4: Pathophysiology of Urinary Incontinence, Faecal Incontinence, and Pelvic Organ Prolapse) at 263-64 (Ex. 2062).

29. OAB significantly affects quality of life – socially, psychologically, occupationally, etc. Paul Abrams et al., *Overactive Bladder Significantly Affects Quality of Life*, AMERICAN JOURNAL OF MANAGED CARE 6:11, S580-S590 at S581 (2000) (hereinafter, "Abrams (2000)") (Ex. 2063). OAB causes sufferers to miss life events in favor of staying confined to their homes or other well-known locations so that they always have reliable access to bathrooms. OAB may cause sufferers to experience embarrassing leakages or be forced to wear pads or diapers as an adult. The adverse effects of OAB may be generally broken down into four categories – coping, concern, adjusted social interaction, and loss of sleep. "Coping" may comprise decreased physical activity, the need to plan activities around the availability of bathrooms, limiting fluid intake, and the wearing of dark clothing. "Concern" may comprise fear, anxiety, worry, loss of self-esteem, or embarrassment about having leakage or other OAB symptoms. "Adjusted Social Interaction" may comprise limiting and planning travel around toilet accessibility, limiting social interactions, and frustrating family and friends. "Sleep" may comprise sleeplessness and fatigue when OAB symptoms interfere with the ability to obtain a full night's rest.

30. In the United States alone, approximately sixteen percent (16%) of adults over the age of 18 years old have overactive bladder. Walter F. Stewart et al., *The prevalence and impact of overactive bladder in the U.S.: results from the NOBLE program,* Neurourol Urodyn. at 406-8 (2001) (Ex. 2064).

B. Muscarinic Receptors

31. Both abnormal and normal bladder contractions occur when acetylcholine, a neurotransmitter, binds to muscarinic cholinergic receptors in the bladder. Several different subtypes of muscarinic receptors are known, classified as M_1-M_5. *See, e.g.*, Karl-Erik Andersson, *The Pharmacological Treatment of Urinary Incontinence*, BJU INTERNATIONAL (1999) 84:932-47 (hereinafter, "Andersson (Review)") (Ex. 1006).

32. The various muscarinic receptor subtypes are found throughout the body in various tissues:

Receptor Subtype	Predominant Location
M_1	Brain, Salivary glands
M_2	Brain, Heart, Bladder, Eyes
M_3	Smooth muscle cells, including bowel and bladder, and glands, including Salivary glands
M_4	Brain, Salivary glands
M_5	Not well known

33. The prevalence of the various muscarinic receptor subtypes varies from tissue to tissue. *See, e.g.*, Lisbeth Nilvebrant et al., *Tolterodine – A New Bladder-Selective Antimuscarinic Agent*, EUROPEAN JOURNAL OF PHARMACOLOGY 327 at 195-96 (1997) (hereinafter, "Nilvebrant II (1997)") (Ex. 2032); Lisbeth Nilvebrant, *Clinical Experiences with Tolterodine*, LIFE SCIENCES 68, 2549-56 at 2549-50 (2001) (hereinafter, "Nilvebrant (2001)") (Ex. 2040); Christopher Chapple & Lisbeth Nilvebrant, *Tolterodine: Selectivity for the Urinary Bladder Over the Eye (as Measured by Visual Accommodation) in Healthy Volunteers*, DRUGS R&D 2002, 3(2): 75-81 at 75-76 (hereinafter, "Chapple (2002)") (Ex. 2065).

34. An antimuscarinic compound, also known as an anticholinergic compound, may have no preference for the muscarinic receptors in the bladder over those present in other tissues and can cause significant side effects in patients. For example, antimuscarinic compounds can inhibit muscarinic receptors in the salivary glands, such as M_3 receptors, and cause dryness of the mouth. *See, e.g.*, Ex. 2032 at 199-206; Ex. 2040 at 2549, 2552-53; *see also* Ex. 2065 at 80. Likewise, antimuscarinic compounds that inhibit muscarinic receptors in the gut can cause constipation, which has been shown to actually aggravate symptoms of OAB. *See, e.g.,* Christopher Chapple, et al., *The Effects of Antimuscarinic Treatments in Overactive Bladder: An Update of a Systematic Review and Meta-*

Analysis, EUROPEAN UROLOGY 54 at 558-559 (2008) (hereinafter, "Chapple (2008)") (Ex. 2066).

35. Antimuscarinic compounds that are highly "lipophilic" can pass through the blood-brain barrier ("BBB") and bind to muscarinic receptors present in the central nervous system ("CNS"), including the brain, potentially causing CNS side effects such as cognitive impairment, dizziness, and somnolence. *See* Ernesto Callegari et al., *A Comprehensive Non-Clinical Evaluation of the CNS Penetration Potential of Antimuscarinic Agents For the Treatment of Overactive Bladder*, BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, 72:2, 235-46 (2011) at 236 (hereinafter "Callegari") (Ex. 2005). CNS side effects can be particularly troublesome for elderly patients, which constitute a significant percentage of OAB sufferers. Ex. 2005 at 236; Ex. 2062 (Committee 4: Pathophysiology of Urinary Incontinence, Faecal Incontinence, and Pelvic Organ Prolapse) at 260 and (Committee 8: Pharmacological Treatment of Urinary Incontinence) at 626-28.

C. Treatment of OAB in 1998

36. Other than pharmaceutical and surgical treatment, persons suffering from OAB had limited options in 1998. These options included adult diapers, or other similar types of pads, to control leakage. Another option included behavior modification, such as limiting the consumption of liquids, mapping the locations of bathrooms, scheduling voiding, and re-training the pelvic floor muscle through

specific exercises. Such options allowed minimal coping, but had significant effects on the patient's quality of life as they could severely limit socialization and even shame and embarrass the patient. *See, e.g.*, Ex. 2063 at S581-82.

37. In 1998, there were two primary pharmaceutical treatments available – oxybutynin and tolterodine. These compounds are both examples of "anticholinergics" or "antimuscarinics" that act by preventing acetylcholine from binding to cholinergic muscarinic receptors. This action relaxes the bladder muscle (or prevents it from contracting), which causes a reduction in a patient's symptoms (including urgency and frequency of urination).

38. Oxybutynin was first approved to treat urinary incontinence in 1975 and has been used as an OAB drug since. Oxybutynin is now available in a variety of forms and formulations, but as of the priority dates, oxybutynin was available only in immediate release and extended release forms (Ditropan® and Ditropan XL®), where the extended release form (Ditropan XL®) was approved in December 1998. FDA, *Drugs@FDA:Ditropan*, https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last visited Oct. 14, 2016) (Ex. 2067).

39. While oxybutynin can be effective in treating OAB, it is associated with substantial side effects characteristic of antimuscarinics, most notably dryness of mouth and constipation, which can render it intolerable for patients. These antimuscarinic side effects are dose dependent, meaning their incidence increases

with an increase in dose. Further, oxybutynin is highly lipophilic, meaning it can cross the blood-brain barrier and enter the CNS; as of the priority dates, oxybutynin was associated with significant CNS side effects. Ex. 2005 at 244; Ex. 2062 (Committee 8) at 649. In 1998, oxybutynin's efficacy and side effect profile were well-known and its usefulness as an OAB treatment was acknowledged as limited. Ex. 2062 (Committee 8) at 655; Karl-Erik Andersson, *Current Concepts in the Treatment of Disorders of Micturition*, DRUGS 35:477-494, 481 (1988) (hereinafter, "Andersson (1988)") (Ex. 2068); Ex. 2040 at 2549; Ex. 1006 at 929-30. Today, many physicians prescribe oxybutynin largely because it is a comparatively inexpensive pharmaceutical option due its availability in generic forms, and because of significant external pressure from third-party payers to prescribe generic medications.

40. Tolterodine, the second primary pharmaceutical treatment available, initially launched in early 1998 as Detrol® (an immediate release or "IR" drug) and was known to clinicians in the IR form as of the priority dates of the patents-in-suit. Later, in 2001, a once-daily, controlled release formulation was launched under the name Detrol® LA.

41. Tolterodine was the first drug specifically designed to treat overactive bladder. Tolterodine has similar efficacy to oxybutynin at comparable dosages, but has a better tolerability and safety profile. This is consistent with preclinical

testing that indicated that tolterodine preferentially binds to muscarinic receptors in the bladder over those in other tissues, such as the salivary glands. *See generally, e.g.*, Ex. 2032; Lisbeth Nilvebrant, *Tolterodine: A New Bladder-Selective Muscarinic Receptor Antagonist*, LIFE SCIENCES 60:1129-37 (1997) (hereinafter, "Nilvebrant III (1997)") (Ex. 2004); Ex. 1006 at 928; Ex. 2040.

42. Tolterodine is only available in 2 and 4 mg daily dosages. The 4 mg dose is the recommended dose. *See* Detrol® LA Prescribing Information, Revised 08/2012, § 2.1 (Ex. 2070). As of the priority dates, Detrol® was only available in 1 and 2 mg IR forms. Detrol® Prescribing Information, Revised 3/1998 (Ex. 1009). The twice daily 2 mg dose was the recommended starting dose at that time. *Id.* at § 7. Higher dosages of Detrol® have never been approved by the Food & Drug Administration ("FDA").

43. In a Phase I study, a 6.4 mg daily dosage of tolterodine was evaluated, but large increases in residual urinary volume and micturition difficulties in several subjects were observed in patients receiving this dosage. *See* M.M.S. Stahl, *Urodynamic and Other Effects of Tolterodine: a Novel Antimuscarinic Drug for the Treatment of Detrusor Overactivity*, NEUROUROL. URO. 14: 647-655 (1995) (Ex. 2069). In a second study, one out of eight subjects receiving a 6.4 mg dosage of tolterodine and six out of eight subjects receiving a 12.8 mg dosage of tolterodine experienced micturition difficulties, which lasted up to sixteen hours

after the administration. Niclas Brynne, et al., *Pharmacokinetics and Pharmacodynamics of Tolterodine in Man: A New Drug for the Treatment of Urinary Bladder Overactivity*, INT'L J. CLIN. PHARMACOLOGY AND THERAPEUTICS, 35:287 at 293 (1997) (hereinafter "Brynne (1997)") (Ex. 1007).

44. Subsequent Phase II clinical trials studied the effects of 4 mg of tolterodine twice daily (among other twice daily dosages). Ex. 2004 at 1134-35. Of the 58 patients who took 4 mg of tolterodine twice daily, four experienced urinary retention, causing them to discontinue treatment, and marked increases in residual volume were observed in patients receiving the 4 mg dose. Urinary retention is a serious side effect that has different meanings to different clinicians, but it generally relates to the patient's ability to empty their bladder efficiently and could lead to kidney failure. Others define retention as the inability to urinate to such a degree that it necessitates insertion of a urethral catheter. For these reasons, a dosage of 4 mg (twice daily) was judged as too high, and only the 1 and 2 mg dosages were advanced into the Phase III clinical program. *Id.* at 1135.

45. In addition to urinary retention, tolterodine's effect on QT interval, a measure of the length of the heart's electrical cycle which, where prolonged, may cause serious cardiac complications, raised concerns. The Detrol® LA label warns that tolterodine is associated with an effect on QT interval. *See* Ex. 2070, § 5.9. Prior to tolterodine's development, terodiline, an OAB drug and chemical analog

of tolterodine and fesoterodine, had been withdrawn from the market in 1991 due to its association with QT effects. Ex. 2062 (Committee 8) at 646; Ex. 1006 at 929. Consequently, QT effects were a concern for entities developing and physicians treating OAB.

46. A clinical study on tolterodine and QT effect assessed twice daily 2 mg and 4 mg IR doses of tolterodine (*i.e.,* total daily doses of 4 mg and 8 mg). The study used moxifloxacin, a compound with a known effect on QT interval, as the positive control or comparator. *See* Ex. 2070, §§ 5.9, 10, 12.2; *see also* Bimal Malhotra et al. *Thorough QT Study with Recommended and Supratherapeutic Doses of Tolterodine*, CLINICAL PHARMACOLOGY & THERAPEUTICS 81:377-385 (2007) ("Malhotra (2007)") (Ex. 2071). Though the approved clinical doses were not found to correspond to a QT effect, the "QT interval prolongation was observed with tolterodine immediate release at doses up to 8 mg[,] and higher doses were not evaluated." Ex. 2070, § 10. The prescribing information further states that "[t]olterodine's effect on QT interval was found to correlate with plasma concentrations of tolterodine" and instructs physicians to consider this issue in prescribing tolterodine to patients with some history of QT prolongation, or who are taking certain other medications that might have an effect on QT. *Id.* §§ 5.9, 12.2. This is consistent with data available as part of the approval package of Detrol, which reflected a dose-dependent increase in QTc prolongation observed in

preclinical studies. Detrol, NDA No. 20-771 Approval Package, Review and Evaluation of Pharmacology (Ex. 2072).

47. While tolterodine is not associated with CNS side effects to the same extent as oxybutynin, it is associated with CNS side effects such as confusion, disorientation, memory impairment, and hallucinations. *See* Ex. 2005 at Tables 1-4; Ex. 2070, §§ 5.5, 6.2.

48. Other than tolterodine and oxybutynin, other pharmaceutical options were available or known in 1998, but were not commonly used or had been withdrawn from the market due to side effect risks. These included propantheline, trospium, imipramine, hyocyamine, and terodiline.

49. As of 1998, the predominant two drugs used by clinicians to treat patients with OAB – tolterodine and oxybutynin – had similar efficacy, but differed primarily in that tolterodine had a more favorable side effect profile and oxybutynin was available in a higher dose. Even though both compounds are antimuscarinics, patients respond differently to each drug, so a patient may be unsuccessful on one compound and find success on the second. While some patients were well-served by these two drugs, many others were not able to obtain relief from their symptoms. Subsequently approved drugs – such as solifenacin (Vesicare®, approved in 2004), darifenacin (Enablex®, also approved in 2004), and transdermal oxybutynin, available as a gel and patch – differed from the

previously available drugs largely in terms of tolerability, but not in terms of efficacy. There was a clear need in 1998 for an OAB treatment that offered "true" dose-escalation – increased efficacy delivered safely and tolerably. It is my opinion that in 1998 clinicians had limited treatment options in helping patients with OAB, it was significantly undertreated, and clinicians needed new and improved treatment alternatives.

VII. FESOTERODINE (TOVIAZ®)

50. Fesoterodine is sold by Pfizer under the trade name Toviaz®. Toviaz® is available as an extended-release, once-daily formulation, in 4 mg and 8 mg daily dosages. Toviaz® prescribing information, revised 8/2012, § 2 (Ex. 1024).

51. Fesoterodine is a prodrug of the compound 5-HMT. 5-HMT is an active metabolite of tolterodine, the active pharmaceutical ingredient in Detrol®. As a prodrug, fesoterodine is itself essentially inactive but is rapidly metabolized in the body into 5-HMT. Martin C. Michel, *Fesoterodine: A Novel Muscarinic Receptor Antagonist for the Treatment of Overactive Bladder Syndrome*, EXPERT OPIN. PHARMACOTHER. 9:1787-96 (2008) (hereinafter, "Michel") (Ex. 2073); Bimal Malhotra, et al., *The Design and Development of Fesoterodine as a Prodrug of 5-Hydroxymethyl Tolterodine (5-HMT), the Active Metabolite of Tolterodine*, CURRENT MEDICINAL CHEMISTRY, 16:33, 4481-89 (2009) (hereinafter, "Malhotra (2009)") (Ex. 2074).

A. Fesoterodine is an Efficacious OAB Treatment

52. The core clinical value of fesoterodine is its dose-flexible efficacy in comparison to the other OAB treatments available. Fesoterodine's clinical efficacy was apparent from the earliest clinical trial results. Phase II clinical studies using daily dosages of 2, 4, 8, and 12 mg found that fesoterodine produced significant improvement in efficacy parameters compared to placebo, and that all doses of fesoterodine were well-tolerated and safe. Ex. 2073 at 1792; Victor Nitti, et al., *Fesoterodine is an Effective Antimuscarinic for Patients with Overactive Bladder (OAB): Results of a Phase 2 Trial* (hereinafter, "Nitti") (Ex. 2075); Christopher Chapple, *Fesoterodine, a New Effective and Well-Tolerated Antimuscarinic for the Treatment of Urgency-Frequency Syndrome: Results of a Phase 2 Controlled Study*, NEUROUROL. URODYN., 23 (5-6) at 598-99 (2004) (hereinafter, "Chapple (2004)") (Ex. 2076); Ex. 2074 at 4487.

53. In Phase III trials, 4 mg of fesoterodine was found to reduce urinary urge incontinence episodes ("UUI") per 24 hours by 67-80% and 8 mg of fesoterodine reduced UUI episodes by 82-88%. Chapple C, Van Kerrebroeck P, Tubaro A, et al. *Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder.* EUR UROL. 52(4):1204-1212 (2007) (Ex. 2077); Nitti VW, Dmochowski R, Sand PK, et al. *Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome.* J UROL. 178(6):2488-2494 (2007)

(Ex. 2078). These results were maintained over two years demonstrating the excellent durability of efficacy and tolerability experienced with Toviaz, mirroring what is seen in clinical practice.

54. In a flexible-dose escalation study with fesoterodine, subjects completed 3-day bladder diaries and the primary end point was change from baseline in number of micturitions per 24 hours at Week 12. Fesoterodine was shown to have a statistically significant effect in reducing the mean number of UUI episodes compared to placebo. Dmochowski RR, Peters KM, Morrow JD, et al. *Randomized, double-blind, placebo-controlled study of flexible-dose fesoterodine in subjects with overactive bladder.* UROLOGY. 75(1):62-68 (2010) (Ex. 2079). In a separate post hoc analysis of the UUI data, it was found that 63% of the fesoterodine group was diary dry; that is, they recorded no UUI episodes in their 3-day bladder diaries at Week 12. *Id.*

55. Fesoterodine has also been proven efficacious in men, even though OAB symptoms in men have historically been associated with enlarged prostates or bladder outlet obstruction and treated accordingly. In a post-hoc analysis of two Phase III clinical studies, fesoterodine 4 and 8 mg were found generally safe, efficacious, and well-tolerated for the treatment of overactive bladder symptoms in men. The 8 mg dose provided additional benefit and allowed for treatment individualization. Sender Herschorn et al., *Efficacy and Tolerability of*

Fesoterodine in Men With Overactive Bladder: A Pooled Analysis of 2 Phase III Studies, J. UROLOGY. 75 (5) 1149-1155 (2010) (Ex. 2080).

B. Toviaz® Has a Favorable Safety and Tolerability Profile

56. The safety and tolerability of fesoterodine were also apparent in early clinical trials. Beyond the Phase II and Phase III studies described above that also assessed the safety and tolerability of fesoterodine, the 8 mg daily dose of fesoterodine was found specifically to not produce significant urinary retention or residual urine volume concerns. *See, e.g.*, Vik Khullar, et al., *Fesoterodine Dose Response in Subjects with Overactive Bladder Syndrome*, FEMALE UROLOGY (2008) ("Khullar (2008)") (Ex. 2081) (urinary retention "occurred in 1% (6 of 554) of subjects in the fesoterodine 4 mg group and 1% (8 of 566) of subjects in the fesoterodine 8 mg group"); *see also* Steve Chaplin and Adrian Wagg, *Fesoterodine (Toviaz): New Option for Overactive Bladder*, PRESCRIBER 5 (2008), *available at* www.prescriber.co.uk (Table 2) (Ex. 2082) (omitting urinary retention from table of adverse events occurring in more than 2% of patients across four clinical studies); Ex. 2076 (Table 2) (omitting urinary retention from table of adverse events for fesoterodine 4, 8 and 12 mg dosages and stating that "all other adverse events were in the range of placebo for all treatment groups").

57. I have reviewed the August 25, 2016 transcript of the deposition of Culley C. Carson, III, M.D., Petitioner's expert urologist in the pending, related

litigation *Pfizer Inc. and UCB Pharma GmbH v. Mylan Pharmaceuticals Inc.*, No. 1:15-cv-000079 (GMS) (D. Del.) ("Carson Tr.") (Ex. 2026). I note that Dr. Carson agreed that a "drug that relaxed the bladder better but had less risk of urinary retention . . . would be a home run." Ex. 2026 at 141:2-5. That very drug is fesoterodine because even at the 8 mg daily dose, it was found to not produce significant urinary retention. *See* Ex. 2081.

58. Fesoterodine was also found to not produce an effect on QT interval. Because of the cardiac safety concerns associated with terodiline and tolterodine, it was necessary to study whether fesoterodine had any effect on QT interval. Bimal Malhotra, et al., *Thorough QT Study of the Effect of Fesoterodine on Cardiac Repolarization*, INT'L J. PHARMACOLOGY & THERAPEUTICS, 48:309-18 (2010) (Ex. 2083). The QT study on fesoterodine evaluated fesoterodine dosages of 4 mg and a not-approved supratherapeutic dose of 28 mg. The supratherapeutic 28 mg dose was chosen because it was previously identified as the maximum tolerated dose of fesoterodine, and constituted the "worst case scenario" of an individual who received an 8 mg dose of fesoterodine yet was unable to metabolize the drug, resulting in atypically high exposure. *Id.* at 310. Neither dose of fesoterodine was found to have any significant effect on QT interval. *Id.* at 314-15, 317-18. Dr. Carson, Petitioner's expert urologist in the pending litigation, agreed during his

deposition that fesoterodine does not have the same concern with respect to QT interval compared to other drugs, including tolterodine. Ex. 2026 at 48:25-49:3.

59. Fesoterodine has been demonstrated to have limited CNS side effects. The effects of fesoterodine 4 mg and 8 mg versus placebo were studied using a wide range of tests that evaluated different elements of cognitive function, including psychomotor function, visual attention, visual learning, visual associative learning, executive function, verbal learning, and memory. Gary Kay et al., *Evaluation of Cognitive Function in Healthy Older Subjects Treated with Fesoterodine*, POSTGRADUATE MEDICINE, Volume 124, Issue 3, 7-15 (May 2012) (Ex. 2084). The two fesoterodine doses were found to have no statistically significant effects compared to placebo on any cognitive function assessed, including memory; whereas alprazolam 1 mg (used as a comparator) produced statistically significant deterioration. *Id.*

60. Further, fesoterodine's ability to cross the blood-brain barrier (a key attribute of drugs that produce adverse CNS side effects) was compared against other OAB treatments including tolterodine, darifenacin, oxybutynin, solifenacin, and trospium. Ex. 2005, at 238. The study included various measures of CNS penetration, including the ratio of brain to plasma concentration of each treatment normalized for their bioavailability. *Id.* at 240. The study showed that fesoterodine was significantly less likely than tolterodine and oxybutynin, among

others, to result in exposure to brain tissue; fesoterodine's brain plasma ratio was 0.16, while tolterodine's was 2.95, or nearly 20x higher, and oxybutynin's was 6.27, or nearly 40x higher. *Id.* This difference may result from the fact that 5-HMT is a substrate of P-glycoprotein ("P-gp"), an efflux transporter that actively pumps compounds out of the brain, while tolterodine and oxybutynin are not. *Id.* at 239, 243.

C. Toviaz® Offered the First "True" Dose-Escalation Treatment Option for Patients

61. Toviaz®'s excellent efficacy and favorable efficacy/safety/tolerability profile has been found to be dose-dependent, thus it has been referred to as offering true dose-escalation. Toviaz® offers physicians the ability to individually treat patients, maximizing efficacy and balancing it with acceptable tolerability and safety. For example, patients with high drug sensitivity may have sufficient efficacy on a lower dose of drug but may experience unacceptable tolerability on a higher dose; conversely, patients with low drug sensitivity may have insufficient efficacy on a lower dose but achieve increased benefit with acceptable tolerability on a higher dose.

62. In the EIGHT trial, fesoterodine 8 mg showed statistically significant superior efficacy compared to fesoterodine 4 mg and placebo, as measured by reductions in UUI episodes, diary-dry rate, micturition frequency, urgency episodes per 24 hours, and improvements in measures of health-related quality of

life and patient reported outcomes without a corresponding increase in side effects. Chapple, C. et al., *Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial*, BRIT. J. UROLOGY INT'L. 114:418-426 (2014) ("Chapple (2014)") (Ex. 2085).

63. Fesoterodine's reputation as a "true" dose-escalation treatment was confirmed in a 2014 analysis of ten publications (six clinical studies) related to flexible-dosing of fesoterodine, which found that 51–63% of subjects initially receiving fesoterodine 4 mg opted for dose escalation to fesoterodine 8 mg. Wyndaele, J.J. et al., *Flexible dosing with fesoterodine 4 and 8 mg: a systematic review of data from clinical trials*, Int'l J. Clin. Prac. 68:7, 830-840 (2014) (Ex. 2086). At baseline, the individuals choosing to escalate the dose ("escalators") generally reported significantly more severe overactive bladder symptoms, greater OAB symptom bother, and worse health-related quality of life at baseline than non-escalators. Escalators reported a lower sensitivity (less efficacy and fewer adverse events) to fesoterodine 4 mg and less treatment benefit than non-escalators at that dosage. However, the study found that escalators experienced improved efficacy after dose-escalation to fesoterodine 8 mg and, therefore, the authors concluded that fesoterodine provides treatment benefit to individual subjects with OAB because of its dose-response effect. *Id.* The results of this study are highly

relevant to clinical practice. I note that Dr. Carson agreed during his deposition that a real benefit of fesoterodine over tolterodine was the ability to dose-escalate. Ex. 2026 at 129:24-130:4.

D. Toviaz® Offers Superior Efficacy

64. A head-to-head, placebo controlled trial (the "Herschorn study") compared the maximum approved daily dosages of fesoterodine and tolterodine (8 mg v. 4 mg, respectively). Sender Herschorn, et al., *Comparison of Fesoterodine and Tolterodine Extended Release for the Treatment of Overactive Bladder: A Head-to-Head Placebo-Controlled Trial*, BJU INT'L, 105:58-66 (2009) (Ex. 2087). The primary endpoint was change in the number of incontinence episodes per 24 hour period over the 12-week study period. Additional quantitative efficacy endpoints and patient-reported outcome questionnaires were included. *Id.*

65. The Herschorn study found that 8 mg of fesoterodine was statistically significantly superior to tolterodine in terms of mean reduction in the number of UUI episodes per 24 hours, as well as diary-dry rate, mean voided volume per void ("MW/void"), Patient Perception of Bladder Condition ("PPBC") score, Urgency Perception Scale ("UPS") score, and the OAB Questionnaire's ("OAB-q") Symptom Bother and total Health-Related Quality of Life ("HRQL") scores. *Id.* at 64. Fesoterodine was also numerically superior to tolterodine in several other

efficacy measures. *Id.* at 61-65. The authors of the study concluded that 8 mg of fesoterodine showed superior efficacy over 4 mg of tolterodine ER. *Id.* at 58.

66. In a second head-to-head trial, patients received: (a) fesoterodine (4 mg for one week, 8 mg for eleven weeks), (b) tolterodine ER 4 mg, or (c) placebo. *See* Steven A. Kaplan, et al., *Superior Efficacy of Fesoterodine over Tolterodine Extended Release with Rapid Onset: a Prospective, Head-to-Head Placebo-Controlled Trial*, BRIT. J. URO. 107, 1432-40 (2010) (hereinafter, "Rapid Onset Study") (Ex. 2088). The results showed superiority of fesoterodine to tolterodine in nearly all efficacy variables. *Id.* at 1437-39. According to the authors, the Rapid Onset study was "the largest double-blind, placebo-controlled, randomized study to compare antimuscarinic efficacy on OAB to date." *Id.* at 1438.

67. A post-hoc analysis of results obtained in a separate, prior study that compared tolterodine and fesoterodine to placebo reached similar conclusions as the Herschorn and Rapid Onset Studies. *See* Christopher Chapple, et al., *Comparison of Fesoterodine and Tolterodine in Patients with Overactive Bladder*, BJU INT'L, 102:1128-32 (2008) (hereinafter, the "Chapple study") (Ex. 2089). In particular, the Chapple study concluded that "the maximum recommended dose of fesoterodine (8 mg) is significantly more effective than the maximum recommended dose of tolterodine ER (4 mg) in improving several important OAB outcomes." *Id.* at 1131.

68. Lastly, the AFTER study evaluated subjects who responded sub-optimally to tolterodine extended release 4 mg and subsequently received fesoterodine 8 mg. *See* Steven A. Kaplan, et al., *Efficacy and Safety of Fesoterodine 8 mg in Subjects with Overactive Bladder after a Suboptimal Response to Tolterodine ER*, INT'L J. CLIN. PRACTICE 68:9, 1065-1073 (2014) (Ex. 2090). The authors concluded that "subjects who responded suboptimally to tolterodine ER 4 mg showed significant improvements in UUI and other OAB symptoms and patient-reported outcomes, with good tolerability, during treatment with fesoterodine 8 mg vs. placebo." *Id.* at 1065.

69. Taken together, these studies show that fesoterodine 8 mg possesses superior efficacy to tolterodine 4 mg, while offering an excellent safety and tolerability profile. These conclusions are consistent with my own experiences in my clinical practice. I note that this is also consistent with the opinion of Dr. Carson, Petitioner's expert urologist in the pending litigation. Ex. 2026 at 113:10-11, 113:17-22 ("[T]here are actually a couple of studies that looked at head-to-head experience between tolterodine max dose and fesoterodine max dose, and it showed that the maximum dose of fesoterodine was more effective.").

VIII. FESOTERODINE SATISFIED A LONG-FELT CLINICAL NEED FOR AN IMPROVED OAB TREATMENT

70. As of the priority dates, there were only two treatments commonly used in the United States for the treatment of OAB – oxybutynin and tolterodine. While

these pharmaceuticals were efficacious for some patients, and remain in use today, they each have failings and a substantial number of patients did not respond or only partially responded to one or both drugs. *See, supra*, ¶¶ 36-49. As a result, there existed a need for a more efficacious OAB treatment that offered a satisfactory tolerability and safety profile. Fesoterodine has addressed that need for many patients. *See, supra*, ¶¶ 61-69 and the studies cited therein (efficacy)) and ¶¶ 50-60 and the studies cited therein (tolerability/safety)).

71. Further, both clinical practice and the literature strongly support that the majority of patients treated with antimuscarinics are still symptomatic on lower dosages, and when given the opportunity, seek a higher dose based on efficacy and tolerability. *See, e.g.,* MacDiarmid, S. *Overactive Bladder: Improving the Efficacy of Anticholinergics by Dose Escalation*, CURRENT UROLOGY REPORTS, 4:446-451 (2003) (Ex. 2091). Fesoterodine demonstrated the ability to dose-escalate between the 4 and 8 mg dosages. *See, supra,* ¶¶ 61-63.

72. The antimuscarinics available at the priority dates suffered from drawbacks that inhibited the ability to dose-escalate. Tolterodine is not FDA-approved at dosages higher than 4 mg due to adverse events such as its potential to cause urinary retention and negatively affect QT interval. *See, supra,* ¶¶ 43-46. Improved efficacy has been demonstrated with higher dosages of oxybutynin, but the correlating increase of side effects, such as dry mouth and constipation, greatly

limit its dose-escalation benefit as a clinically practical matter. *Id.* This lack of a clear efficacy/tolerability/safety profile and dose-response relationship and benefit had resulted in dose escalation not being routine in clinical practice despite the well-known need. Ex. 2081 at 839.

73. After the priority date, the ability to dose-escalate was pursued in the development of various other antimuscarinics, but only Toviaz® offers increased efficacy to such a degree with a higher dose that it is statistically superior to the lower dose in fixed dose studies. For example, the authors of Chapple (2014) concluded that "[f]ixed-dose studies of various pharmacological OAB treatments have typically not shown a statistically significant dose-response effect for the reduction of OAB symptoms or have shown a dose-response effect only over a short (4-week) period." Ex. 2085 at 419. I agree with this conclusion of Chapple (2014).

74. Ultimately, only fesoterodine, and its higher 8 mg dose, has been demonstrated to be statistically significantly superior to a lower FDA-approved dosage of that drug in fixed-dose Phase III placebo-controlled studies. *See, supra,* ¶¶ 61-63. Moreover, fesoterodine allows for this increased dosage without significantly increasing the risk of side effects. This finding is significant because it demonstrates the effectiveness of the 8 mg dosage and strongly supports the use of Toviaz in the individualization of therapy in clinical practice, an option that was

not otherwise available as of the priority date with the options available – oxybutynin and tolterodine – and that is not met by other OAB treatments available even today.

75. Fesoterodine was compared against tolterodine, the other drug that was available to patients at the priority dates, in head-to-head clinical trials and other analyses. *See, supra,* ¶¶ 64-69. These studies demonstrated that fesoterodine effectively delivers greater efficacy than tolterodine in a safe, tolerable way. As explained *supra*, the primary problem with the OAB treatments that were available before Toviaz® is that they exhibited few, if any, differences in terms of efficacy. If a patient did not respond to a given drug, it was possible to try others, but without any ability to predict whether switching treatments would provide a meaningful reduction in symptoms. Toviaz® met this need for a more efficacious treatment by, for example, demonstrating statistically significant superior clinical efficacy over the market leader at the time of its launch, Detrol® LA, and efficacy in patients who were sub-optimal responders to Detrol® LA. *See, supra,* ¶ 68. For the numerous patients who failed to respond to Detrol® LA, or other treatments on the market, Toviaz® addressed this substantial unmet need. I can confirm based on my own clinical practice that an 8 mg daily dose of fesoterodine is the best option for treating many OAB patients.

76. I have found Toviaz® to offer clinical benefits to many patients who were unsuccessful on other drugs, including Detrol®, and it has affected my clinical treatment of OAB. In my opinion, Toviaz 8 mg is an exceptional OAB therapy and is one of the most important tools urologists have for the treatment of overactive bladder. Further, in clinical practice, when a patient fails one antimuscarinic agent based on efficacy and/or tolerability, they may respond favorably to other OAB agents. Based on the prior art, it was not obvious that if a patient failed on Detrol® that they would benefit from Toviaz®. In the AFTER study, it was found that subjects who were "sub-optimal" responders to Detrol® 4 mg responded favorably to Toviaz® 8 mg.

IX. FESOTERODINE HAS SEVERAL UNEXPECTED BENEFICIAL PROPERTIES THAT COULD NOT HAVE BEEN PREDICTED

77. Fesoterodine's markedly different clinical profile, including its demonstrated heightened efficacy and ability to deliver a higher dose, was a surprise to the urological community at large. *See, supra,* ¶¶ 61-69. It was not possible to reliably predict fesoterodine's clinical profile prior to a full clinical development program, and certainly not possible to predict how fesoterodine would perform compared to tolterodine.

78. Moreover, nobody could have predicted that fesoterodine's increased efficacy would come with a favorable safety and tolerability profile. This is especially true for side effects associated with tolterodine considering the shared

active metabolite, 5-HMT. Whereas an 8 mg supratherapeutic dose of tolterodine was found to be associated with urinary retention in Phase II trials such that Phase III trials were not pursued (*see, supra,* ¶¶ 43-44), fesoterodine does not cause similar urinary retention concerns at the same dose (*see, supra,* ¶¶ 56-57 and studies cited therein). Similarly, whereas other diphenylpropylamine antimuscarinics such as terodiline and tolterodine are associated with significant effects on QT intervals, fesoterodine is not. *See, supra,* ¶¶ 45-46 (regarding terodiline and tolterodine) and ¶ 58 (regarding fesoterodine). For this reason, unlike tolterodine, the FDA-approved label for fesoterodine does not include warnings regarding QT prolongation.

79. Finally, though it has not been the subject of a formal head-to-head study, fesoterodine has limited CNS side effects with a lower incidence than oxybutynin. *See, supra,* ¶ 39 (CNS regarding oxybutynin) and ¶¶ 59-60 (CNS regarding fesoterodine). Given that they share the same active metabolite, it was particularly surprising that fesoterodine is significantly less likely than tolterodine to result in exposure to brain tissue. *See, supra,* ¶¶ 59-60. The reason 5-HMT may result in less exposure in the brain could be attributed to the surprising finding that 5-HMT is a substrate of P-gp, while tolterodine is not. Ex. 2005.

80. I am not aware of anything in the prior art before the studies discussed above with fesoterodine that suggested or would have permitted one to predict that

fesoterodine possesses these surprising properties, especially when compared to tolterodine. Given the importance of these side effects to various clinical populations (e.g., CNS side effects and the elderly (*see, supra,* ¶ 35)), fesoterodine's favorable side effect profile provides a significant and unexpected benefit over previously available drugs.

I hereby declare that statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I reserve the right to revise or supplement my opinions as additional information becomes available. I declare under penalty of perjury that the foregoing Declaration is true and correct.

October 21, 2016

Scott A. MacDiarmid