UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TORRENT PHARMACEUTICALS LIMITED
Petitioner

v.

UCB PHARMA GMBH
Patent Owner

Patent No. 6,858,650
Filing Date: November 15, 2000
Issue Date: February 22, 2005
Title: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Inter Partes Review No. Unassigned

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*

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I. INTRODUCTION

Through counsel, real party in interest Torrent Pharmaceuticals Limited ("Petitioner") hereby petitions for initiation of *inter partes* review of U.S. Patent No. 6,858,650, entitled "STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES" ("the '650 patent"). Ex. 1001.

II. MANDATORY NOTICES

A. Real Party in Interest

Torrent Pharmaceuticals Limited is the real party in interest. Torrent Pharmaceuticals Limited is related to Torrent Private Limited, which is also related to the Torrent Group. Out of an abundance of caution, Torrent Pharmaceuticals Limited identifies the foregoing entities, each of which agrees to be estopped under the provisions of 35 U.S.C. §§ 315 and/or 325 as a result of any final written decision in the requested IPR to the same extent as Petitioner, as real-parties-in-interest, solely to avoid disputes related to this Petition.

B. Related Matters

The '650 patent is asserted in the actions styled: *Pfizer, Inc. and UCB Pharma GMBH v. Mylan Pharmaceuticals, Inc*., No. 1:15-cv-00079-GMS (D. Del.), *Pfizer Inc. and UCB Pharma GMBH v. Mylan Pharmaceuticals Inc*., No. 1:15-cv-00013-IMK (N.D. W. Va.), and *Pfizer, Inc. and UCB Pharma GMBH v. Sandoz, Inc., et al*., No. 1:13-cv-01110-GMS (D. Del.). Petitioner is not a party to any of these actions, and Patent Owner has not asserted the '650 patent against

Petitioner to date.

The '650 patent is the subject of a petition for *inter partes* review (IPR2016-00510) filed by Mylan Pharmaceuticals Inc. and Mylan Laboratories Limited (collectively, "Mylan") on February 2, 2016, which was instituted on July 20, 2016 as to claims 1-5 and 21-24. Petitioner seeks joinder with that IPR for the reasons expressed in the concurrently-filed Motion for Joinder under 35 U.S.C. § 315(c), 37 C.F.R. §§ 42.22 and 42.122(b).

C. Fee

This petition for *inter partes* review is accompanied by a payment of $23,000.00 and requests review of 9 claims of the '650 patent. *See* 37 C.F.R. § 42.15. Thus, this petition meets the fee requirements under 35 U.S.C. § 312(a)(1).

D. Designation of Lead Counsel and Request for Authorization

Petitioner designates lead and back-up counsel as noted below. Powers of attorney pursuant to 37 C.F.R. § 42.10(b) accompany this Petition.

Lead Counsel	Backup Counsel
Neal Seth, Reg. No. 67,075 nseth@wileyrein.com	Lawrence Sung, Reg. No. 38,330 lsung@wileyrein.com
WILEY REIN LLP 1776 K Street NW Washington, DC 20006, Phone: 202.719.7000 / Fax: 202.719.7049	

E. Service Information

As identified in the attached Certificate of Service, a copy of the present

petition, in its entirety, is being served to the address of the attorney or agent of record. Torrent may be served at its counsel, Wiley Rein LLP, at the e-mail addresses indicated above.

F. Standing

Petitioner certifies that the '650 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

III. STATEMENT OF RELIEF REQUESTED

Pursuant to 35 U.S.C. § 311, this petition requests *inter partes* review and cancellation of claims 1-5 and 21-24 of the '650 patent as follows.

(1) Claims 1-5 and 21-24 are invalid as obvious over the Postlind and Bundgaard publications in view of the Detrol® label and Berge.

(2) Claims 1-5 and 21-24 are invalid as obvious over the Brynne 1998 and Bundgaard publications in view of Johansson.

The '650 patent issued from patent application 10/130,214, filed as PCT/EP00/11309 ("the PCT application") on November 15, 2000, designating the U.S. Ex. 1001. The PCT application claimed priority to German application DE 119 55 190, filed November 16, 1999. *Id.* The effective filing date of the '650 patent is November 15, 2000 and the critical date under 35 U.S.C. § 102(b) is November 15, 1999.

Postlind, Ex. 1010, was published in April 1998, was received February 11, 1997, and accepted January 9, 1998. It is prior art under 35 U.S.C. §§ 102(a)-(b).

Bundgaard, Ex. 1012, was published in 1985 and thus is prior art under 35 U.S.C. §§ 102(a)-(b).

The Detrol® label, Ex. 1009, was approved for commercial distribution on March 25, 1998, and thus is prior art under 35 U.S.C. §§ 102(a)-(b).

Johansson, WO 94/11337, Ex. 1005, was published May 1994 and thus is prior art under 35 U.S.C. §§ 102(a)-(b).

Berge, Ex. 1013, was published in 1977 and thus is prior art under 35 U.S.C. 35 U.S.C. §§ 102(a)-(b).

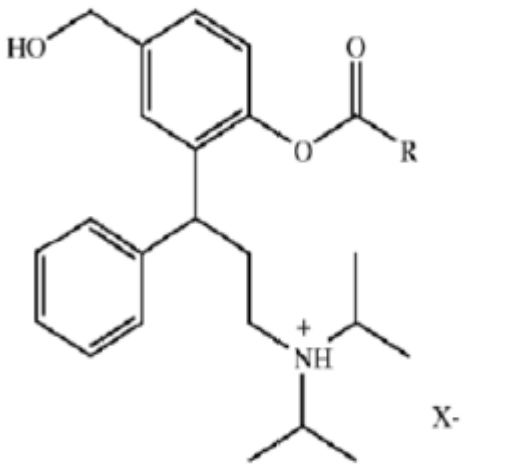
Brynne 1998, Ex. 1011, was presumed published on May 1, 1998, and mailed before May 11, 1998, and thus is prior art under 35 U.S.C. §§ 102(a)-(b).

Before the invention date, Postlind disclosed effective treatment of overactive bladder by use of the 5-hydroxymethyl metabolite of tolterodine ("5-HMT"). From both Postlind and the Detrol® label, the art was also aware that tolterodine was quite effective, but not across all patients and with negative side-effects, in part because catalysis of tolterodine varied across patients. Skilled artisans would thus conclude that use of tolterodine could be improved. Given the active metabolite was known, the catalytic activity was known, and the accepted efficacy of the 5-HMT "prodrug-like" starting compound, the art demonstrates it

would have been obvious to a person of ordinary skill in the art at the time of invention to make a single, suggested modification (Bundgaard) to the active metabolite to achieve the claimed compound. All other aspects of the challenged claims such as salt choice, etc., would naturally follow the development of a pro-drug with a known, desired active metabolite.

IV. SUMMARY OF THE '650 PATENT AND CHALLENGED CLAIMS

The '650 patent describes derivatives of 3,3-diphenylpropylamines and salt forms. Ex. 1001, 1:10-14. Claim 1 provides a generic structure for the covered molecule reproduced here. According to the claim, "R denotes C_1-C_6 –alkyl, C_3-C_{10}-cycloaklyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid." *Id.* at claim 1.



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Claims 2-5 further specify the type of compatible acid (claims 2 and 4), adding specific chirality (claim 3), and two specific substitutions and salt forms (claim 5). Specifically, claim 5 lists R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate. This

is commonly referred to as fesoterodine fumarate. Ex. 1003 ¶ 13. Claims 21-24 recite methods of use.

V. CLAIM CONSTRUCTION

The claims in the '650 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. 37 C.F.R. § 42.100(b).

VI. TECHNICAL BACKGROUND AND STATE OF THE ART

A. The Person of Ordinary Skill in the Art of the '650 Patent

A person of ordinary skill in the art would have a Ph.D. in chemistry, medicinal chemistry, pharmacology, or a related field, and at least one year of industrial exposure to drug discovery, drug design, and synthesis. In lieu of an advanced degree, the individual may have additional years of industry experience, including, for example, in drug discovery, drug synthesis, and structure-activity work. Ex. 1003 ¶ 23.

B. Before the Invention, Antimuscarinic Compounds Were Used to Treat Overactive Bladder Conditions.

Long before the invention, it was known muscarinic receptors play a role in urinary bladder smooth muscle contractions and salivary activity. Ex. 1003 ¶¶ 26-34; Ex. 1010 at 289. The FDA had approved antimuscarinic agents for the treatment of overactive bladder, including tolterodine tartrate marketed under the name Detrol®. Ex. 1009. Detrol® was approved for commercial distribution on

March 25, 1998, and its label described the oxidation of tolterodine by cytochrome P450 2D6 to 5-HMT. Ex. 1025 at 4. Detrol®'s label further states that "[b]oth tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter[s] . . . ." Ex. 1009 at 2.

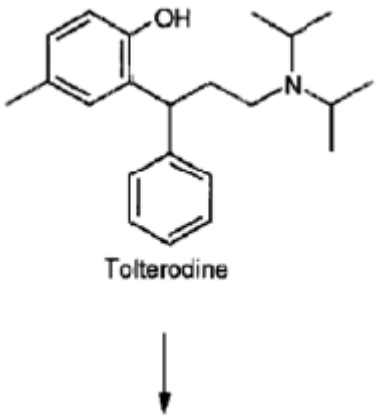
Tolterodine was the first drug specifically developed to treat overactive bladder and thus distinguished itself from another prior art antimuscarinic compound, oxybutynin. Ex. 1014 at 528. Unlike tolterodine, oxybutynin led to dry mouth because it had a higher selectivity for muscarinic receptors on salivary glands over receptors in the bladder. Ex. 1015 at 4. Tolterodine, and its primary, beneficial metabolite 5-HMT, had selectivity for the bladder over receptors on salivary glands and thus tolterodine exhibited a clinical advantage over oxybutynin. *Id.*; Ex. 1017 at 1; Ex. 1007 at 287-88.

An antimuscarinic compound with selective affinity for the bladder naturally garnered focus from skilled artisans.[1] That focus was further sharpened given that tolterodine's label revealed that a subset of the population had poor metabolism by

[1] As explained *infra*, before the invention, other compounds that were not antimuscarinic compounds – calcium antagonists, potassium channel antagonists, and α-adrenoreceptors – were unproven as effective overactive bladder treatment. *See also* Ex. 1003 ¶¶ 26-34.

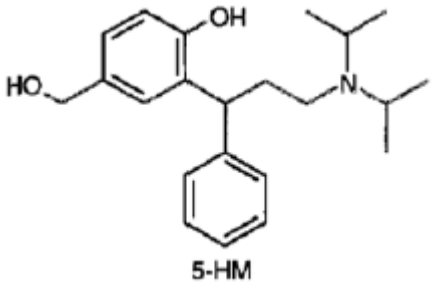
the cytochrome catalyst and thus negligible concentrations of 5-HMT in patients' plasma. Ex. 1009 at 2. Artisans also knew tolterodine possessed its own activity separate from the 5-HMT metabolite and, when present in the serum, could lead to adverse events or negative drug-drug interactions. *Id.* at 2, 7; Ex. 1007 at 291 ("Tolterodine was associated with a dose-dependent increase in heart rate, the onset of which was fairly rapid with time to maximal effect around 1.3 – 1.8 h.").

Prior art identified the main metabolic pathways of tolterodine in human liver microsomes. Ex. 1003 ¶¶ 36, 40, 44, and 48-50. Andersson described how tolterodine undergoes stepwise oxidation of the 5-methyl group to yield the 5-HMT metabolite. Ex. 1014 at 534. Specifically, as shown, the cytochrome catalyst (P450 2D6) oxidizes the 5-methyl to convert tolterodine into its structurally similar active metabolite. *Id.* at Fig. 6 (Andersson); Ex. 1003 ¶¶ 68-69.



Postlind expressly noted that the identification of the metabolic catalyst and mechanism "is of great importance to predict potential drug interactions and genetic variations in drug metabolism." Ex. 1010, 289. It was known that phenotypical differences arising from polymorphism of the cyctochrome catalyst (i.e., CYP2D6) affect a

number of drugs including receptor antagonists and lead to interpatient variability of the efficacy of drugs that are acted on by this pathway. Ex. 1010 at 292; Ex. 1003 ¶ 95-99. Postlind further confirmed that CYP2D6 is responsible for the necessary oxidation to convert tolterodine to its active metabolite, 5-HMT. Ex. 1010 at 292.



5-HM

C. Prodrugs Were Known to Solve Active Compound Difficulties.

Prodrug optimization of known active compounds has been considered an industrially beneficial avenue of drug design for decades. Economic factors often drive decisions which impact drug development. Those factors include market size (number of compounds in a treatment field); medical use amount (number of prescriptions likely to be written in the treatment field); and likelihood of distinguishing a new product from existing compounds beyond non-inferiority. Ex. 1003 ¶¶ 74-76 and 102. The ability to demonstrate required safety and efficacy of an entirely new compound may require wholly independent data collection that would be unneeded or at least limited if prodrug optimization were pursued. Ex. 1026 at 5.

Prodrug optimization thus focuses on active compounds already known rather than examining compounds with untested, undemonstrated efficacy and

safety. Ex. 1003 ¶¶ 80, 106-109. Indeed, skilled artisans were aware of many examples of approved prodrugs of known active compounds that reused and repurposed the underlying data of the active compound. *Id.* ¶¶ 108-109. The use of prodrugs was likewise long known to improve difficulties associated with administering compounds. *Id.* ¶ 80; Ex. 1012 at 1-2. For example, a compound that was too water soluble would lack sufficient lipophilicity to enter the gut wall and be absorbed. Ex. 1003 ¶¶ 112-113; Ex. 1012 at 1-2. This was known to directly impact bioavailability. Ex. 1003 ¶ 112.

Given the known characteristics of 5-HMT, namely its poor lipophilicity (Ex. 1011 at 538), as well as the knowledge of the skilled artisan of the use of prodrug optimization to achieve better bioavailability through increasing lipophilicity, the skilled artisan would have considered 5-HMT a good candidate for prodrug optimization. Ex. 1003 ¶¶ 110-120.

First, the skilled artisans would have known that 5-HMT had bioavailability concerns. Tolterodine, the "prodrug-like" compound to 5-HMT was ten times more lipophilic than the active metabolite—5-HMT. Ex. 1011 at 538; Ex. 1003 ¶¶ 55, 116-118. Skilled artisans also knew that the lipid solubility, and, hence absorption of many polar drug molecules may be improved by forming esters with short or long chain aliphatic acids. Ex. 1012, Ex. 1003 ¶¶ 56-62. Thus, skilled artisans at the time of the invention would have understood from the relationship

between 5-HMT and its metabolic analog tolterodine that modifying 5-HMT would likely provide the necessary protection for the prodrug to pass through the gut and be acted on by enzymes for conversion to the desired active compound. Ex. 1003 ¶¶ 110-119.

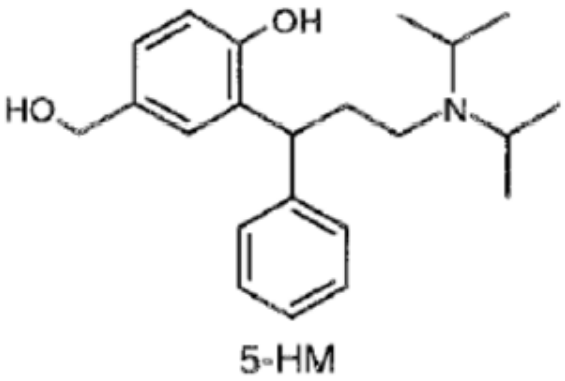
Second, skilled artisans would have known that such optimization of compounds for improved bioavailability by protecting compounds from degradation or improvising gut absorption had been a routine and predictably successful approach since the late 1990s. *Id.* As Bundgaard explained,

> Prodrug research matured as a branch of pharmaceutical research during the 1970s. Over the past decade this chemical approach to optimization of drug delivery has undergone considerable expansion, largely as a result of an increased awareness and understanding of the physicochemical factors that affect the efficacy of drug delivery and action. Several drugs are now used clinically in the form of prodrugs, and as the prodrug approach is becoming an integral part of the new drug design process one may expect that the new drugs in many cases will appear as prodrugs.

Ex. 1012 at Preface. Even more relevant here, skilled artisans knew to create prodrugs containing esters when the desired active metabolite possessed a hydroxyl or carboxyl group. *Id.* at 2 ("In the past, esters mostly have been considered as prodrug types, and the best known prodrugs are in fact esters of drugs containing hydroxyl or carboxyl groups.").

5-HMT would have been an immediate candidate for prodrug modification to the skilled artisan because "[t]he popularity of using esters as a prodrug type for

drugs containing carboxyl or hydroxyl functions (or thiol groups) stems primarily from the fact that the organism is rich in enzymes capable of hydrolyzing esters." *Id.* at 3-4. 5-HMT



5-HM

contains hydroxyl groups (as shown above). Ex. 1010. In fact, the presence of the –OH groups on the #2 and #5 carbons are the primary candidates for prodrug optimization because when an ester group is hydrolyzed in the body, the result is an –OH group. Ex. 1003 ¶¶ 110-12. As such, conversion of the –OH groups to esters as a prodrug optimization are limited to the two –OH groups on 5-HMT. *Id.*

D. Numerous Salt Forms Were Known for Compounds Similar to the Most Effective Overactive Bladder Drugs.

Skilled artisans in 1998 knew that stabilizing compounds through the use of salt forms was an iterative, routine process. Ex. 1027. The commercially available administered compound for 5-HMT was a tartrate salt. Ex. 1009. Oxybutynin was administered as a hydrochloride salt form. Ex. 1003 ¶ 27.

Likewise, multiple texts for drug development described how to select and make salt forms of compounds for drug use. For example, Gould teaches how to identify useful salts and prepare compounds including the hydrate forms. Ex. 1027. Gould explains the benefits and outcomes of ester modification of a drug for prodrug form explains that "[f]or a drug having ionizable functional groups, salt

formation can be a powerful tool in improving formulation properties. Salt formation is preferable to covalent derivatization when the physiochemical property-related problem is one affecting only the formulation, since salt formation is readily reversible upon dissolution in vivo." *Id.*

Finally, the number of approved salt forms was generally limited. Ex. 1013. But, here, the candidate list was even smaller. The FDA approved label for tolterodine disclosed an organic salt and other prior art publications disclosed a substitutable genus that would have included the fumarate salt of 5-HMT. Ex. 1003 ¶¶ 131-132; Ex. 1005 at 2:9-10.

VII. SCOPE AND CONTENT OF THE PRIOR ART

Under *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415-16 (2007), there can be no rigid, formulary test to determine obviousness, instead it requires consideration of the scope and content of the prior art as viewed by the person of ordinary skill in the art. In chemical cases, "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). "[I]t is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). "[P]roving a

reason to select a compound as a lead compound depends on more than just structural similarity, ***but also knowledge in the art of the functional properties and limitations of the prior art compounds***." *Id.* (emphasis added) (citing *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 471 F.3d 1369, 1377-79 (Fed. Cir. 2006)).

A. Skilled Artisans Had Ample Motivation to Focus on Optimizing 5-HMT to Obtain an Overactive Bladder Compound.

1. Postlind, the Detrol® Label, and Brynne 1998 Taught 5-HMT Was an Effective Compound for Overactive Bladder without Tolterodine.

Tolterodine's label explained that it was "metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a majorly pharmacologically active metabolite."[2] Ex. 1009 at 2, Clinical Pharmacology. From its launch, tolterodine informed the art that tolterodine's well-documented metabolism to 5-HMT was associated with two concerns. *Id.*; Ex. 1003 ¶¶ 34, 36-39. First, there was a portion of the population that showed undesirable metabolism because of polymorphism in the enzymatic metabolism of tolterodine. Ex. 1003 ¶¶ 95-98; *Par Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1197-98 (Fed. Cir. 2014) (upholding motivation when prior art suggested suitable options, not necessarily best options, to avoid interpatient variability). Second, tolterodine itself was active. It thus possessed possible side effects and could lead to negative drug-drug interactions should the patient require other medications. Ex. 1003 ¶¶ 95-98;

[2] That metabolite was known as 5-HMT.

Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1373-74 (Fed. Cir. 2005) (prior art's detail on adverse effects of prior compounds supported obviousness).

At the time of the invention, tolterodine had been shown to be a potent compound for the treatment of overactive bladder. Ex. 1003 ¶¶ 40, 48, 66, 68, 71, 74. How it treated overactive bladder conditions and metabolism was scrutinized, in part, because of the immediately known imperfections with the compound. *Id.* ¶¶ 92-95. Between the label and known prior art, the problem for skilled artisans was well characterized, specifically: ***Could tolterodine's active metabolite 5-HMT be improved to obtain better efficacy across all patients while eliminating tolterodine's possible adverse effects?***

This known problem naturally would lead a skilled person to focus on 5-HMT, particularly given the well-known characteristics of 5-HMT. Ex. 1003 ¶¶ 95-102. Skilled persons were fully informed of the functional properties of tolterodine and its active metabolite 5-HMT. *Id.* ¶¶ 99-101. Artisans were also fully aware of drawbacks associated with dosing with tolterodine and, given the efficacy of 5-HMT, would try to take advantage of the active metabolite. *Id.* ¶¶ 95-98. Given the amount of metabolism of tolterodine into 5-HMT, a person of ordinary skill in the art would thus recognize that a solution to both the polymorphism concern and the separate activity of tolterodine would be to try to take advantage of 5-HMT's activity separate from tolterodine. *Id.*

2. Skilled Artisans Would Immediately Recognize the Benefit to Starting with their Knowledge of 5-HMT and Tolterodine and Not Other Compounds.

Patent Owner may argue that the skilled artisan would not focus on 5-HMT to arrive at a compound for treating overactive bladder because it was not the best candidate or best performer and thus a bad target for modification. This is incorrect. Before the invention, the primary FDA-approved overactive bladder compounds were antimuscarinics. *Id.* ¶ 92. Tolterodine and its 5-HMT metabolite act on muscarinic receptors in classes M2 (generally heart) and M3 (bladder, colon, and salivary glands). Ex. 1015 at 172; Ex. 1016 at Table 4. Oxybutynin, an exclusively M3 specific compound, had negative side-effects such as dry mouth, which led to patient noncompliance, thus limiting efficacy. Ex. 1017 at 94. Accordingly, at the time of the invention the skilled person would not have focused on M3 exclusive antimuscarinic compounds because tolterodine's predecessor had demonstrable side effects worth avoiding. Ex. 1003 ¶¶ 92-93.

Classes of compounds other than antimuscarinics did not possess the demonstrated clinical efficacy of antimuscarinic compounds. *Id.* ¶¶ 85-91. Calcium antagonists and potassium channel antagonists were unproven for the treatment of overactive bladder. *Id.* Likewise, there was no established efficacy of α-adrenoreceptors. *Id.*

Pre-invention date compounds available on the market or in development

that had shown potential for use in treating overactive bladder, but which were not specifically aimed at overactive bladder, were similarly less desirable. For example, propantheline was not approved for overactive bladder, was less effective than oxybutynin, and had similarly undesirable side effects. *Id.* A product containing terodiline had been withdrawn from the market in Europe because of severe heart complications. *Id.*; Ex. 1008 at 53. Trospium had poor bioavailability and had not been approved by FDA in 1998. Ex. 1016 at 353. Compounds such as solifenacin and darifenacin had not been tested clinically and had no known bioavailability. Ex. 1003 ¶ 91.

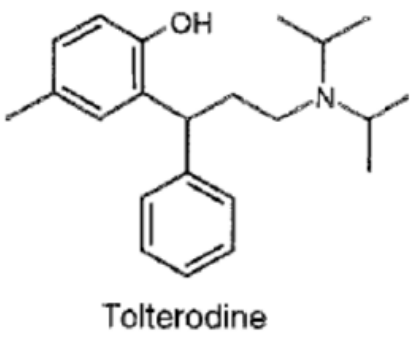
Thus, the skilled person would have ample suggestion and motivation from the prior art to focus on 5-HMT, given its "prodrug-like" administration via tolterodine and would have recognized that it was the best candidate for a skilled artisan to begin an investigation of possible overactive bladder treatment compounds. *Id.* ¶¶ 95-102.

B. Bundgaard Taught Predictable Modifications to Improve 5-HMT Delivery.

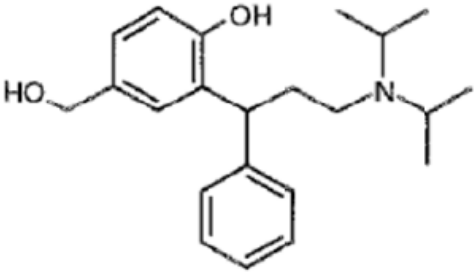
As explained *infra*, skilled persons were well aware of the process for and benefits of prodrug optimization. Multiple commercially approved and marketed drugs had been improved or replaced because the active metabolite of the previously administered compound underwent prodrug modification to avoid issues with the originally administered compound. For example, Allegra® is the

currently marketed prodrug of a carboxylic acid derivative of the previous administered compound terfenadine, which was known to have adverse side effects. Ex. 1018 at 118-19. Similarly, Bundgaard described the well-known use of prodrugs to improve ampicillin in several modifications to increase the bioavailability of the active moiety and produce several commercial compounds. Ex. 1012 at 4-5.

Bundgaard also taught skilled persons that, for active compounds with hydroxyl groups and insufficient bioavailability, esterification increased lipophilicity and thus bioavailability. Ex. 1003 ¶¶ 57-60. Indeed, by the time of the invention, curing problems with lipophilic associated bioavailability of active compounds was a matter of routine optimization through the prodrug modification process. *Id.* ¶¶ 113-122. Examples abounded of successfully modifying active compounds to arrive at prodrugs so as to assist with lipophilic associated bioavailability via the use of esters for the prodrug where the active moiety has an hydroxyl or carboxyl group. *Id.* ¶ 114. The use of esters was attractive because esterases are prevalent in the body and will cause ample conversion of the prodrug to active. *Id.* ¶ 112; Ex. 1012.

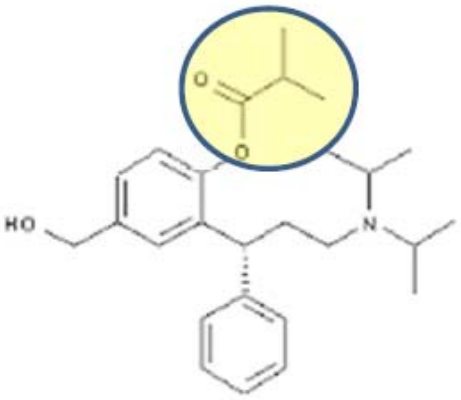


Tolterodine



5-HM

Bundgaard's teachings of such predictable and successful modifications would have been recognized as particularly applicable to 5-HMT. As shown, the structures of tolterodine (top) and 5-HMT (bottom) were well known and differed only in that 5-HMT had a non-hydroxylated methyl group on the left most aromatic ring. Ex. 1003 ¶ 115. The prior art informed the artisan that tolterodine was tenfold more available after first pass (absorption by the gut) than 5-HMT. Ex. 1003 ¶¶ 116-118; Ex. 1011 at 535-36. Thus, skilled persons would immediately recognize that administering unmodified 5-HMT, without tolterodine, would result in limited bioavailability, particularly given 5-HMT's chemical structure. Ex. 1003 ¶ 115.



Prodrug optimization would likely have started with just the two hydroxyl groups on the left most aromatic ring. But, taken with the known ability of esters to successfully modify the hydroxyl groups of active moieties to improve absorption, the immediately obvious position for use of an ester would be on the #2 carbon on the left aromatic ring of

5-HMT shown here. The #2 carbon would be examined first for several reasons. Ex. 1003 ¶¶ 120-129. In prodrug development, if the potential transformation ultimately requires more metabolic steps, or alters the compounds' known pharmacological properties, release of the desired active becomes less optimal. *Id.* ¶¶ 107, 114. Likewise, transesterification concerns would have suggested modifying the #2 carbon hydroxyl group because of steric bulk. *Id.* ¶ 125.

Selection of the ester type would have similarly been from a very limited pool of options. It was well known to use small chain esters with two to six carbon atoms, and specifically known to use the ester of fesoterodine—isobutyric ester. Ex. 1003 ¶ 129; Ex. 1020 (eight esters tested were all short chain, including isobutyryl, and increased permeability and delivery was improved by significant amounts). Optimizing the use of an ester would have focused on monoesters because it was known that diesters could result in too much lipophilicity. Ex. 1003 ¶ 123. Recognizing these known substitutions and adhering to "Pfizer's Rule of 5," which provided guiding principles for drug design based on structural analogs including focus on lipophilicity of compounds for optimizing bioavailability with predictable medicinal chemical results, would yield routine steps of optimization in using esters to replace the hydroxyl on the #2 carbon. *Id.* ¶ 121.

C. Berge and Johansson Taught Fumarate Salts.

The Federal Circuit long has recognized that salt forms come from a limited

genus because of FDA approval of usable salts. *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1362-63 (Fed. Cir. 2007). Berge 1977, relied on by the Court in *Pfizer*, disclosed fumaric acid as an approved salt. Ex. 1013. Other references make it clear that selecting a salt is a matter of routine experimentation and the Federal Court has noted that "a skilled chemist at the time would simply make ***known*** pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working." *Pfizer*, 480 F.3d at 1362.

5-HMT had been studied in its salt form by Johansson, including both the hydrochloric and fumarate salt of 5-HMT. Ex. 1005. Given the extremely straightforward nature of the prodrug modifications to 5-HMT, a person of ordinary skill in the art would recognize that the fumarate and hydrochloric salts would obtain the desired stability of the product for administration and handling. Ex. 1003 ¶¶ 131-137.

VIII. DETAILED GROUNDS FOR UNPATENTABILITY

A. Claims 1-5 are Obvious Over the Postlind and Bundgaard Publications in view of the Detrol® Label and Berge.

Claims 1-5 are invalid as obvious over the Postlind and Bundgaard publications in view of the Detrol® label and Berge. Ex. 1003 ¶¶ 99-102. Claim 1 encompasses fesoterodine fumarate as one of the plurality of alternative embodiments. *Id.* ¶ 13. Fesoterodine fumarate has the chemical name 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen

fumarate. In particular, Formula I of claim 1 embraces fesoterodine wherein R is C_{1-6} alkyl (in particular C_3 alkyl) and X- is the acid residue of fumarate, which is an organic acid. As Formula I does not indicate a particular stereoisomeric form, it is interpreted as being generic to either the R- or the S-stereoisomer. Thus, claim 1 embraces fesoterodine fumarate.

Claims 2 and 3 depend from claim 1 and further limit the subject matter of claim 1. Claim 2 further defines X- is the acid residue of, *inter alia*, fumaric acid which corresponds to the "fumarate" anion of fesoterodine fumarate. Claim 3 further defines the compound of Formula I as belonging to the subgroup of Formula 2, which is a particular stereoisomer of the compound recited in Formula I. When R is isopropyl and X- is the acid residue of fumaric acid, the compound of Formula 2 is fesoterodine fumarate.

Claim 4 depends from claim 3, and thus further limits the subject matter of claim 3 by defining X- is the acid residue of, *inter alia*, fumaric acid, which corresponds to the "fumarate" anion of fesoterodine fumarate.

Claim 5 depends from claim 4 and recites a Markush group of two compounds, one of which, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate, which is synonymous with fesoterodine fumarate.

1. <u>A Person of Ordinary Skill Would Have Been Motivated to Look at Improved 5-HMT Administration in View of</u>

Tolterodine

5-HMT was known to be an effective treatment for urinary incontinence. The Prescribing Information for Detrol® (brand name for tolterodine) describes 5-HMT as the active metabolite responsible for the therapeutically beneficial antimuscarinic activity in the bladder as follows:

> After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect.

Ex. 1009 at 2, Clinical Pharmacology; Ex. 1003 ¶¶ 36-39.

A person of ordinary skill in the art would have elected to begin with 5-HMT to address its interplay with tolterodine instead of other marketed overactive bladder compounds or beginning anew for the reasons detailed above. *See supra* § VII.A. Specifically, the marketed products were less effective than 5-HMT and tolterodine, had problems/side effects, or would have meant starting completely over. *Id.* Choosing a lead compound does not ignore the skilled artisan's knowledge and consider treatment options without understanding the field; rather, it is the opposite—it accounts for the properties and limitations of the prior art to determine if a compound stands out as a logical, even if not the most logical, choice. *Daiichi*, 619 F.3d at 1354.

The Postlind reference would have motivated a person of ordinary skill to

modify 5-HMT to a compound that avoided CYP2D6 metabolism as known to occur with tolterodine. Ex. 1010. Postlind teaches that the metabolism of tolterodine to 5-HMT proceeds through the CYP2D6 enzyme in the liver, and that 80% of tolterodine is metabolized to 5-HMT. *Id.* at 292. Postlind notes that previous clinical studies (with other drugs) demonstrate that individuals with lowered CYP2D6 metabolism represent a high-risk group in the population with propensity to develop adverse side effects. *Id.*

> Clinical studies have demonstrated that individuals with reduced CYP2D6-mediated metabolism represent a high-risk group in the population with a propensity to develop adverse drug effects. The number of drugs identified as being affected by CYP2D6 polymorphism has increased steadily over the years and includes diverse classes such as β-adrenoreceptor antagonists, tricyclic antidepressants, neuroleptics, and other miscellaneous drugs like dextromethorphan and codeine.
>
> . . .
>
> The possibility of clinical drug interaction at the enzyme level thus exists, especially if tolterodine is administered at the same time as a compound that is preferentially metabolized by CYP2D6 or to individuals associated with the CYP2D6 poor metabolizer phenotype.

Id. (internal citations omitted)

Postlind thus informed skilled artisans that the major metabolite of tolterodine in normal humans is 5-HMT, that the metabolism of tolterodine to 5-HMT proceeds via the CYP2D6 pathway in the liver, and that various factors, such as polymorphism and/or inhibition of CYP2D6 by concurrently administered drugs, may result in decreased metabolism of tolterodine to 5-HMT and an

increased incidence in adverse side effects in the affected subpopulation. Ex. 1003 ¶¶ 40-43. This cytochrome polymorphism interaction is confirmed in Prescribing Information for Detrol®, which requires a dose adjustment to prevent adverse events in these patients. Ex. 1009 at 7 ("For patients with significantly reduced hepatic function or who are currently taking drugs that are inhibitors of cytochrome P450 3A4, the recommended dose is 1 mg twice daily (see PRECAUTIONS, General).") Accordingly, a person of ordinary skill in the art would have appreciated the 5-HMT compound was a great candidate for overactive bladder treatment and sought to modify the compound to avoid CYP2D6 metabolism and the risk of drug interaction and adverse effect associated with administering tolterodine. Ex. 1003 ¶¶ 95-102.

2. Postlind and Bundgaard Publications in View of the Detrol® Label and Berge Would Have Led to Prodrug Optimization and Fumarate Salt Forms.

Because the Prescribing Information for Detrol® and Postlind identify the active compound and the unfavorable route of metabolism (and associated complications) of tolterodine, a person skilled in the art would have been motivated to identify a way to build on the known activity of the 5-HMT compound in a way to develop a compound that would avoid the CYP2D6 metabolism problem of tolterodine. Thus, a skilled artisan would have been motivated to consider the well-known potential of prodrug methodology used to

alter drug metabolism and optimize drug delivery. Ex. 1003 ¶¶ 105-112.

As of 1998, a skilled artisan would have been very familiar with prodrugs. Prodrug design is an area of drug research that focuses on the optimization of drug delivery. Ex. 1012 at Preface, v. For example, Bundgaard, a prodrug textbook published in 1985, described a prodrug as a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug. *Id.* According to Bundgaard:

> A molecule with optimal structural configuration and physiochemical properties for eliciting the desired therapeutic response at its target site does not necessarily possess the best molecular form and properties for its delivery to its point of ultimate action. Usually, only a minor fraction of doses administered reaches [sic] the target area and, since most agents interact with non-target sites as well, an inefficient delivery may result in undesirable side effects. This fact of differences in transport and in situ effect characteristics for many drug molecules is the basic reason why bioreversible chemical derivatization of drugs, *i.e.*, prodrug formation is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved.

Id. at Preface v-vi. Given the understanding that prodrugs would allow for optimized delivery of an already identified compound, a person of skill in the art would have considered developing a prodrug of the 5-HMT compound in view of the known properties of tolterodine. Ex. 1003 ¶¶ 112-118. Moreover, certain guiding principles governed how prodrug optimization occurred. For example, it was always desired to make the fewest modifications of the known active so as to not add more metabolic steps to achieve the active once administered. *Id.* ¶ 114.

This is because the more changes to the active the less likely the new drug would possess the same, known functionality. *Id.*

Similar to the modification necessary for 5-HMT, Bundgaard explains that:

> Active drug species containing hydroxyl or carboxyl groups can often be converted to prodrug esters from which the active forms are regenerated by esterases within the body, e.g., in the blood. In other cases, active drug substances are regenerated from their prodrugs by biochemical reductive or oxidative processes. Sulindac, for example, is active only when reduced to its thioether form [1,2] and a prodrug of the pyridinium quaternary compound, 2-PAM, is converted to the parent drug through an enzymatic oxidation process in the body.

Ex. 1012 at 1-2.

As described above (Ex. 1003 ¶¶ 116, 118), a person of ordinary skill in the art would have appreciated that 5-HMT was too lipophilic and needed to be modified in a way to improve bioavailability. Thus, preparing an ester prodrug would have been an obvious choice to modify 5-HMT. Bundgaard teaches that esterification of a compound containing a hydroxyl group makes it "feasible to obtain derivatives with almost any desirable hydrophilicity or lipophilicityas well as in vivo lability." Ex. 1012 at 4. Even more compelling, Bundgaard also discloses the synthesis of prodrugs from compounds with many of the same functional groups found in 5-HMT. Ex. 1003 ¶¶ 119-120; Ex. 1012 at Table 2.

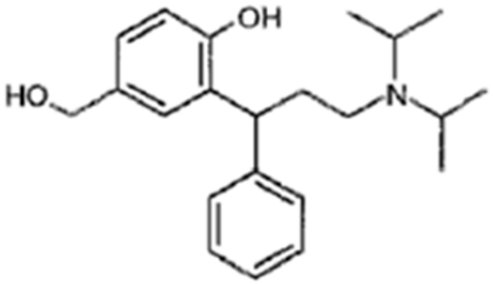
TABLE 2
Examples of Ester Derivatives Developed as Prodrugs for Drugs Containing a Hydroxyl Group

Drug	Ester	Reference
Salicylic acid	Carboxylate and carbonate esters	59, 60
Paracetamol	Carbonate esters	61, 62
	Phosphate ester	63
Trichloroethanol	Carbonate esters	64, 65
	Phosphate ester	66
Cymarol	Diacetylester	67
Vidarabine	Mono- and diesters	68, 69
	Phosphate ester	70
Thymidine	Pivaloate	71
Oxazepam, lorazepam	Aliphatic and aromatic esters	72 – 74
	Amino acid esters	75
Metronidazole	Aromatic esters	76 – 78
	Phosphate ester	79
	Amino acid esters	80, 81
Chloramphenicol	Palmitate and hemisuccinate	82
Various steroids	Various esters	19
Phenols	Amino acid esters	83
Lincomycin	Dialkylcarbonate esters	84
Epinephrine	Dipivaloate	85
Etilefrine	Aliphatic and aromatic esters	86
2-Amino-6,7-dihydroxytetrahydronaphthalene (6,7-ADTN)	Various diesters	87
Terbutaline	Mono- and diesters	88
Isoproterenol	Ditoluyl and dipivaloyl esters	89
Cytarabine	Various mono- and diesters	90
Digitoxigenin	Amino acid esters	91
Acyclovir	Amino acid and hemisuccinate esters	92

Table 2 shows multiple, successful examples of ester derivatives developed as prodrugs for drugs containing a hydroxyl group. This evidence confirms skilled artisans would have been motivated to improve 5-HMT by preparing an ester prodrug as described in Bundgaard especially given the greater than reasonable chance of success. *Id.*

As described above, a person of skill in the art would have known the chemical structure for 5-HMT. A skilled artisan evaluating 5-HMT would have

appreciated there was a limited set of only two primary locations to reasonably consider modifying—the #2 and #5 - position carbon on the left most aromatic ring. Ex. 1003 ¶¶ 125-130. These hydroxyl groups would have been the focus because those groups contribute to the relatively low lipophilicity of 5-HMT. *Id.* ¶¶ 110, 115-116. But the skilled artisan would have been further motivated to focus on the #2 position carbon because of what the skilled artisan could glean from comparing the "prodrug-like" tolterodine with 5-HMT. *Id.* ¶¶ 116-120. The difference between the 5-position of the two known prior art compounds is a methyl and a hydroxymethyl group. Because the metabolism of tolterodine to 5-HMT changed the methyl to a hydroxymethyl, and it was known that this metabolism took place via the CYP2D6 pathway, a person of skill in the art would avoid modifications to the #5 position. *Id.* ¶¶ 125-130.



5-HM

The presence of the hydroxyl group at the 2-position of 5-HMT would lead the skilled artisan to consider modifications to this position that would result in a hydroxymethyl in this position after metabolism in the body. *Id.* ¶¶ 119, 124. A protecting ester would have been an obvious modification in view of the prior art. *Id.* Specifically, Bundgaard reference provides the motivation to prepare an ester prodrug of hydroxyl-containing active compounds such as 5-HMT. These esters

were known to possess useful properties, such as complete hydrolysis to form the hydroxyl-containing active compound *in vivo* and improved pharmacokinetic properties, such as improved lipophilicity, and oral uptake compared to the active hydroxyl-containing parent compound. Ex. 1012 at 4.

Bundgaard even discloses using carbonate or monoesters to make such a modification in Table 2. The skilled artisan would have simply optimized the monoester at the #2 carbon with short chain esters and arrive at the isobutyl ester. Ex. 1003 ¶¶ 119-120. A finding of obviousness is required where the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention". . .. *Takeda*, 492 F.3d at 1356 (citation omitted).

Finally, the disclosure of an acid addition salt does not render claims 1-5 non- obvious. The Federal Circuit has recognized salt forms come from a limited genus because of FDA approval of usable salts. *Pfizer*, 480 F.3d at 1362-63.

Berge, which the *Pfizer* court relied upon, teaches:

> The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound.
>
> Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a

> particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility and formulation profiles.

Ex. 1013 at 1. Berge expressly aimed "to present an overview of the many different salts which new drug candidates can be chosen and to assemble data that will provide, for the student and practitioner alike, a rational basis for selecting a suitable salt form." *Id.* at 1-2. Berge's Table 1 lists the salts approved by the FDA as of the publication date of the reference. Ex. 1003 ¶¶ 64-65.

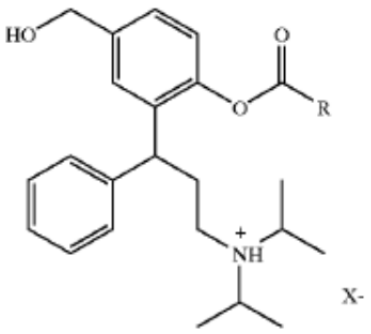
Berge disclosed fumaric acid as an approved salt. Ex. 1013 at 2; *Pfizer*, 480 F.3d at 1355 ("Table 1 of Berge shows 53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts, and lists the relative frequency of which each was used as a percentage based on the total number of anions or cations in use through 1974."); *id.* at 1363 ("This is true especially given the fact that the genus of FDA-approved anions at the time was small, *i.e.*, only 53").

3. Summary of Proposed Rejection of Claims 1-5

At the time of the invention, the skilled artisan knew the functional properties of 5-HMT and knew 5-HMT was a key active metabolite of tolterodine. They also knew the limitations of the "prodrug-like" administration of tolterodine. As a result of this interplay, and the structural similarity between 5-HMT and

tolterodine, a person of ordinary skill would (1) focus on 5-HMT as a lead compound based on the Detrol® label and Postlind and (2) apply Bundgaard's prodrug optimization and Berge's known salts to obtained the esterified version of 5-HMT. *Daiichi*, 619 F.3d at 1354. Indeed, in light of what was known about the "prodrug"-like administration of tolterodine application of prodrug methodology was simple routine optimization. *Eli Lilly*, 471 F.3d at 1379; *see also In re Applied Materials*, 692 F.3d 1289, 1297-98 (Fed. Cir. 2012) (holding routine optimization is part of the *KSR* obviousness analysis).

The table below summarizes the proposed rejection for claims 1-5:

Claim	Correspondence to the Prior Art
1. Compounds of general formula I  in which R denotes C_1- C_6-alkyl, C_3 -C_{10} - cycloalkyl, substituted or unsubstituted phenyl and X^3 - is the acid residue of a physiologically compatible inorganic or organic acid.	**1) 5-HMT** • "After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect." (Ex. 1009 at 2, Clinical Pharmacology)(label). • "Tolterodine is extensively metabolized by the liver

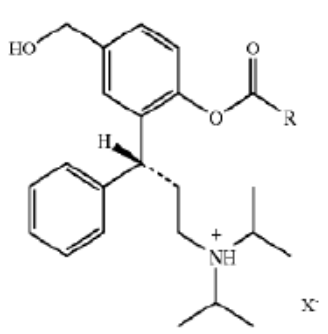
	following oral dosing. The primary metabolic route involves the oxidation of the 5-methly group and is mediated by the cytochrome P450 2D6 and leads to the formation of the pharmacologically active 5-hydroxymethyl metabolite." (Ex. 1009 at 2, Metabolism)(label). • "A subset (about 7%) of the population is devoid of cytochrome P450 2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine." (Ex. 1009 at 2, Metabolism)(label). • "Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite." (Ex. 1009 at 2, Metabolism)(label). • "We conclude from these studies that the formation of 5-HM is catalyzed by CYP2D6 and that the formation of N-dealkylated tolterodine is predominantly

	catalyzed by CYP3A isoenzymes in human liver microsomes." (Ex. 1010 at Abstract)(Postlind). • "Strong correlation was found between the formation of the 5- hydroxymethyl metabolite of tolterodine (5-HM) and CYP2d6 activity (r2, 0.87), as well as between the formation of N-dealkylated tolterodine and CYP3A activity (r2, 0.97)." (Ex. 1010 at Abstract)(Postlind). • "Clinical studies have demonstrated that individuals with reduced CYP2D6-mediated metabolism represent a high-risk group in the population with a propensity to develop adverse drug effects." (Ex. 1010 at 292)(Postlind). • "CYP3a is the major P450 subfamily in human liver and is involved in the metabolism of >50% of pharmaceutical drugs on the market. In addition, CYP3A enzymes have been reported to be involved in interactions with several drugs such as macrolides, ketoconazole, cyclsporin, and others." (Ex. 1010 at 292) (internal citations omitted) (Postlind).

	2) Prodrug • "In the past, esters mostly have been considered as prodrug types, and the best known prodrugs are in fact esters of drugs containing hydroxyl or carboxyl groups." (Ex. 1012 at 2) (Bundgaard). • "The popularity of using esters as a prodrug type for drugs containing carboxyl or hydroxyl functions (or thiol groups) stems primarily from the fact that the organism is rich in enzymes capable of hydrolyzing esters)." (Ex. 1012 at 3-4)(Bundgaard). • "In addition, by appropriate esterification of molecules containing a hydroxyl or carboxyl group it is feasible to obtain derivatives with almost any desirable hydrophilicity or lipophilicity as well as in vivo lability, the latter being dictated by electronic and steric factors." (Ex. 1012 at 4)(Bundgaard). • "Prodrug research matured as a branch of pharmaceutical research during the 1970s. Over the past decade this chemical approach to

	optimization of drug delivery has undergone considerable expansion, largely as a result of an increased awareness and understanding of the physiochemical factors that affect the efficacy of drug delivery and action. Several drugs are now used clinically in the form of prodrugs, and as the prodrug approach is becoming an integral part of the new drug design process one may expect that the new drugs in many cases will appear as prodrugs." (Ex. 1012 at Preface v-vi (Bundgaard). • Active drug species containing hydroxyl or carboxyl groups can often be converted to prodrug esters from which the active forms are regenerated by esterases within the body, e.g., in the blood. In other cases, active drug substances are regenerated from their prodrugs by biochemical reductive or oxidative processes. Sulindac, for example, is active only when reduced to its thioether form [1,2] and a prodrug of the pyridinium quaternary compound, 2-PAM, is converted to the parent drug through an enzymatic oxidation process in the

	body. (Ex. 1012 at 1-2) (Bundgaard). • Ex 1012 at 3, Table 2) (Bundgaard). **3) Salts** • "Our purpose is twofold: to present an overview of the many different salts which new drug candidates can be chosen and to assemble data that will provide, for the student and practitioner alike, a rational basis for selecting a suitable salt form." (Ex. 1013 at 1-2)(Berge). • "Salt formation is an acid-base reaction involving either a proton- transfer or neutralization reaction and is therefore controlled by factors influencing such reactions. (Ex. 1013 at 2)(Berge). • Table 1 FDA-Approved Commercially Marketed Salts discloses the fumarate salt. (Ex. 1013 at 2)(Berge).
2. Compounds in accordance with claim 1, characterised in that X- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic	**See claim 1 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology)(label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); (Ex.

acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)- malic acid, DL-tartaric acid, L-(+) - tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)- ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.	1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). **Salt Formation** • "Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions." (Ex. 1013 at 2)(Berge).
3. Compounds in accordance with claims 1, characterised in that they have general formula 2: Formula 2  in which R denotes C_1 -C_6 -alkyl, C_3 –C_{10} -cycloalkyl, substituted or unsubstituted phenyl and X^3 is the acid residue of a physiologically compatible inorganic or organic acid.	**See claim 1 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology)(label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). **(R) enantiomer** • "Tolterodine [(R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-phenylprpanamine] is a new muscarinic receptor antagonist specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289) (Postlind).
4. Compounds in accordance with claim 3,	**See claims 1 and 3 above,**

characterised in that X in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL- malic acid, L-(-)-malic acid, D-(+)- malic acid, DL-tartaric acid, L-(+)- tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)- ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.	**incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology)(label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1010, Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); Ex. 1010 at 289)(Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). **Salt Formation** • "Salt formation is an acid-base reaction involving either a proton-transfer or neutralization reaction and is therefore controlled by factors influencing such reactions." (Ex. 1013 at 2) (Berge).
5. Compounds in accordance with claims 3, characterised in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl -phenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1- phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.	**See claims 1 and 3 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology)(label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); Ex. 1010 at 289)(Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2) (Berge). **(R) enantiomer** • "Tolterodine [(R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-phenylprpanamine] is a new muscarinic receptor antagonist

	specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289) (Postlind).

B. Claims 21-24 are Obvious over the Postlind and Bundgaard Publications in view of the Detrol® Label and Berge.

Claim 21 depends from claim 1 and recites a method of treating a patient suffering from urinary incontinence, in which the method comprises the step of administering to said patient an effective amount of a compound of Claim 1. Claim 22 depends from claim 3 and recites a method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to the patient an effective amount of a compound according to claim 3. Claim 23 is closely related to claim 22 reciting a method of treating a patient suffering from urinary incontinence, and the method comprises the step of administering to the patient an effective amount of a compound according to claim 5. Claim 24 also depends from claim 5 and further limits the treatment of urinary incontinence to urge incontinence.

As discussed above, 5-HMT was known as an effective compound for the treatment of urinary incontinence by exerting antimuscarinic activity in the bladder. Ex. 1009 at 2. Claim 1 recites a prodrug of 5-HMT. As disclosed in Bundgaard, a prodrug is pharmacologically inactive, and is quickly metabolized to

its active form. *Id.* at 1 ("The prodrug per se is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug. For example, prodrugs designed to overcome solubility problems in formulating intravenous injection solutions should preferably be converted immediately to drug following injection so that the concentration of circulating prodrug would rapidly become insignificant in relation to that of the active drug.") Thus, skilled artisans would have expected the use of the compound in claim 1 to be quickly metabolized to the active compound, 5-HMT, which was well known to be beneficial for the treatment of urinary incontinence. Ex. 1003 ¶¶ 138-139.

With respect to urge incontinence recited in claim 24, Detrol®'s Prescribing Information identifies the product as beneficial for the treatment of urge incontinence. Ex. 1009 at 5 ("Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence"). As discussed above, the active metabolite responsible for the efficacy of Detrol® is 5-HMT. *Id.* ("The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect.") As such, a skilled artisan would expect that the treatment with the compound of claim 1, 3 or 5, all of which form 5-HMT, to be beneficial for urge incontinence. Ex. 1003 ¶¶ 138-139.

The table below summarizes the proposed rejection for claims 21-24:

21. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.	**See claim 1 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology)(label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2 (Berge). • "Tolterodine [(R)-N,N- diisopropyl-3-2-hydroxy-5- methylphenyl)-penylprapanamine] is a new muscarinic receptor antagonist specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289)(Postlind) (internal citations omitted). • The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. (Ex. 1009 at 2, Clinical Pharmacology) (Detrol label).
22. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.	**See claims 1, 3, and 21 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology) (label); (Ex. 1009 at 2, Metabolism)(label); (Ex. 1009 at Abstract) (Postlind); (Ex. 1010 at 292) (Postlind); Ex. 1010 at 289)(Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). • "Tolterodine [(R)-N,N- diisopropyl-3-)2-hydroxy-5- methylphenyl)-penylprapanamine] is a new muscarinic receptor antagonist specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289)(Postlind) (internal citations omitted). • The 5-hydroxymethyl metabolite, which

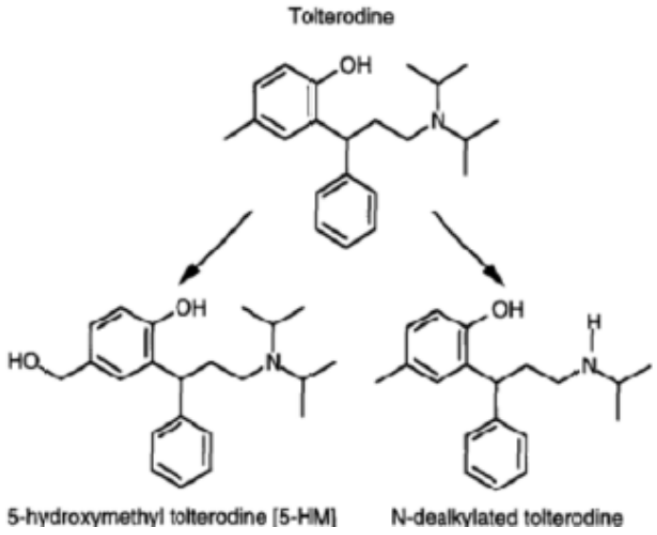
	exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. (Ex. 1009 at 2, Clinical Pharmacology) (Detrol® label).
23. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.	**See claims 1, 3, 5, and 21 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology) (label); (Ex.1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); Ex. 1010 at 289)(Postlind); (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). • "Tolterodine [(R)-N,N-diisopropyl-3-)2-hydroxy-5-methylphenyl)-penylprapanamine] is a new muscarinic receptor antagonist specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289)(Postlind) (internal citations omitted). • The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. (Ex. 1009 at 2, Clinical Pharmacology) (Detrol® label).
24. The method of any one of claims 21-23, wherein the urinary incontinence disorder is urge incontinence.	**See claims 1, 3, 5, and 21 above, incorporated herein.** (Ex. 1009 at 2, Clinical Pharmacology) (label); (Ex.1009 at 2, Metabolism)(label); (Ex. 1010 at Abstract)(Postlind); (Ex. 1010 at 292) (Postlind); Ex. 1010 at 289)(Postlind); (Ex. 1010 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1013 at 1-2)(Berge). • "Tolterodine [(R)-N,N-diisopropyl-3-)2-hydroxy-5-methylphenyl)-penylprapanamine] is a new muscarinic

	receptor antagonist specifically developed for the treatment of urinary urge incontinence and other symptoms associated with overactive bladder." (Ex. 1010 at 289)(Postlind) (internal citations omitted). • The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. (Ex. 1009 at 2, Clinical Pharmacology) (Detrol label).

C. Claims 1-5 and 21-24 Are Rendered Obvious by Brynne 1998, Bundgaard, and Johansson.

1. A Person of Ordinary Skill Would Have Been Motivated to Look at Improved 5-HMT Administration in View of Tolterodine.

As detailed above, 5-HMT was known to be an effective treatment of urinary incontinence. More specifically, Brynne 1998 teaches that 5-HMT was active metabolite of tolterodine metabolism via the CYP2D6 pathway. Ex. 1011 at 529. Brynne 1998 details that variations in the metabolism of tolterodine can result in either an active metabolite (5-HMT) or an inactive N-dealkylated tolterodine. *Id.* at 530. As described, a skilled person would have elected to begin with 5-HMT



because of its known efficacy and ability to avoid administering tolterodine. *See supra* at VII.A.

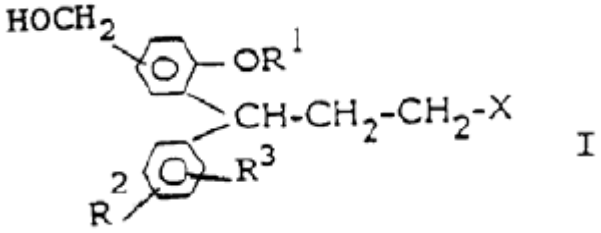
Brynne 1998 further documented the benefits of avoiding dosing with tolterodine because "there was a correlation between tolterodine concentration and the effect on salivation . . . ." Ex. 1011 at 538. Accordingly, a person of ordinary skill would have been motivated to take the teachings of Brynne 1998 and focus on the 5-HMT active metabolite as a compound for modification. Ex. 1003 ¶¶ 100-102.

2. Brynne 1998 in View of Bundgaard and Johansson Would Have Led to Prodrug Optimization and Fumarate Salt Forms.

Brynne 1998 investigated the metabolic pathway of tolterodine to 5-HMT. Critically, it discloses that "tolterodine is tenfold more lipophilic than 5-HM, and consequently tolterodine penetrates membranes more rapidly." Ex. 1011 at 538. Given 5-HMT's attractiveness as a starting point, the ordinarily skilled artisan would have been further motivated to follow prodrug methodologies given the lipophilicity issues of 5-HMT detailed in Brynne. Ex. 1003 ¶¶ 105-108. As discussed above, prodrugs were well known to address tissue penetration issues due to lipophilicity. Ex. 1003 ¶¶ 112-118. Bundgaard specifically identifies the use of esterification to increase bioavailability of compounds with poor lipophilicity. *See supra*, VII.A.2.

Johansson (WO 94/11337) makes it more predictable that the prodrug of 5-

HMT in a fumarate salt would be successfully achieved. Ex. 1003 ¶¶ 133-137. Johansson taught the formation of a fumarate salt in a genus containing 5-HMT. *Id.* Johansson was published on May 26, 1997. Johansson teaches compounds of the general formula:



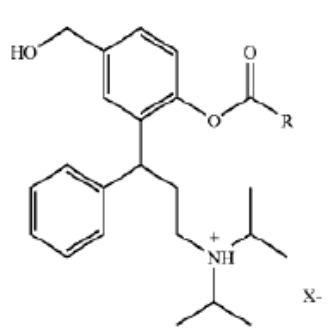
I

which through described substitutions arrives at 5-HMT. *Id.* The Johansson reference also taught that, "the compounds of formula I can form salts with physiologically acceptable acids." Ex. 1005 at 2:5-6. Specific "examples of such acid addition salts included the ***hydrochloride***, hydrobromide, hydrogen ***fumarate***, and the like." *Id.* at 2:8-10. Both the hydrochloride and fumarate salts are claimed in the instant patent. This same compound is disclosed and claimed in U.S. Patent 5,686,464, which is a divisional application of Johansson.[3]

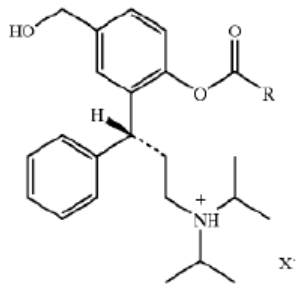
Thus, taken together, Brynne 1998, Bundgaard, and Johansson would have motivated a person of skill in the art to start with 5-HMT and follow know prodrug

[3] Because the patent to the 5-HMT compound was available as of November 1997, this is an additional reason that a person of skill in the art in 1998 would have been motivated to research and investigate a different compound. Ex. 1003 ¶ 136.

optimization and salt optimization to arrive at fesoterodine fumarate.

1. Compounds of general formula I  Formula I in which R denotes C_1- C_6-alkyl, C_3 - C_{10} -cycloalkyl, substituted or unsubstituted phenyl and X^3 - is the acid residue of a physiologically compatible inorganic or organic acid.	**See the claim chart above for ground 1 related to Bundgaard**. (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); **5-HMT** • "Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency or urge incontinence." (Ex. 1011 at 530)(Brynne). • "Two hepatic oxidative metabolic pathways have been identified – hydroxylation and N-dealkylation (Fig. 1)." (*Id*.). • "Preclinical studies have shown that the 5-hydroxymethyl metabolite (5-HM) of tolterodine (PNU-200577) is pharmacologically active and equipotent compared with tolterodine in vitro." (*Id*.). • "There was a distinct difference in serum tolterodine concentrations between the panels of the extensive metabolizers and those of the poor metabolizers." (*Id*. at 532 -33; *see also* Tables 1 and 2). • "In previous studies, it was concluded that the effect on stimulated salivation after tolterodine administration was mainly derived from an active unknown metabolite and that there was a tenfold difference in serum protein binding between tolterodine

	and 5-HM (fraction unbound [f_u] of tolterodine, 3.7%, and f_u of 5-HM, 36%)." (*Id*. at 535-36). • "This study showed that tolterodine is extensively metabolized by CYP2D6. The high specificity is shown by the fivefold difference in CL between the two panels and the fact that poor metabolizers showed no quantifiable serum levels of 5-HMT." (*Id*. at 536). • "Tolterodine is tenfold more lipophilic than 5-HM, and consequently tolterodine penetrates membranes more rapidly." (*Id*. at 538). **Salts** • "The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." Ex. 1005 at 2:5-10) (Johansson). • "These metabolites have at least as favourable anti-cholinergic properties as the parent compounds and can thus be used for the control of events mediated by acetylcholine, like urination." (*Id*. at 1:13-17).
2. Compounds in accordance with claim 1, characterised in that X^- in	***See* claim 1 above, incorporated herein** (Ex. 1012 at Preface v-vi, 1-4, Table 2)

each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)- malic acid, DL-tartaric acid, L-(+) - tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)- ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.	(Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17)(Johansson). **Salts** • "The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." (Ex. 1005 at 2:5-10)(Johansson) • "These metabolites have at least as favourable anti-cholinergic properties as the parent compounds and can thus be used for the control of events mediated by acetylcholine, like urination." (*Id.* at 1:13-17).
3. Compounds in accordance with claims 1, characterised in that they have general formula 2:  in which R denotes C_1 -C_6 -alkyl, C_3–C_{10} -cycloalkyl, substituted or unsubstituted phenyl and X^3 is the acid residue of a physiologically compatible inorganic or organic acid.	**See claim 1 above, incorporated herein.** (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17) (Johannson). **Enantiomers** • "iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, . . ." (Ex. 1005 at 6:4-5)(Johansson). • "The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by

	fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns." (*Id.* at 6:24-28).
4. Compounds in accordance with claim 3, characterised in that X in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DLmalic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.	**See claims 1 and 3 above, incorporated herein.** (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17; 6:4-5; 6:24-28) (Johansson). **Salts** • "The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." (Ex. 1005 at 2:5-10)(Johansson). • "These metabolites have at least as favourable anti-cholinergic properties as the parent compounds and can thus be used for the control of events mediated by acetylcholine, like urination." (*Id.* at 1:13-17).
5. Compounds in accordance with claims 3, characterised in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl -phenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1- phenylpropyl)-	**See claims 1 and 3 above, incorporated herein.** (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17; 6:4-5; 6:24-28)(Johansson). **Enantiomers**

4- hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.	• "iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, . . ." (Ex. 1005 at 6:4-5)(Johansson). • "The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns." (*Id.* at 6:24-28). • The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." (*Id*. at 2:5-10).
21. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.	**See claim 1 above, incorporated herein.** (Ex. 1012, Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17)(Johansson). • "Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency and urge incontinence." Ex. 1011 at 530. • "Preclinical studies have shown that tolterodine has high antimuscarinic potency in guinea pig and human

	detrusor muscle and displays favorable selectivity for the urinary bladder over salivary glands in vivo." *Id*.
22. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.	**See claims 1 and 3, incorporated herein.** (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17; 6:4-5; 6:24-28)(Johansson). • "Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency and urge incontinence." Ex. 1011 at 530. • "Preclinical studies have shown that tolterodine has high antimuscarinic potency in guinea pig and human detrusor muscle and displays favorable selectivity for the urinary bladder over salivary glands in vivo." *Id*.
23. A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.	**See claims 1, 3, and 5, incorporated herein.** (Ex. 1012 at Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17; 6:4-5; 6:24-28)(Johansson). • "Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency and urge incontinence." Ex. 1011 at 530. • "Preclinical studies have shown that

	tolterodine has high antimuscarinic potency in guinea pig and human detrusor muscle and displays favorable selectivity for the urinary bladder over salivary glands in vivo." *Id*.
24. The method of any one of claims 21-23, wherein the urinary incontinence disorder is urge continence.	**See claims 1, 3, and 5, incorporated herein.** (Ex. 1012, Preface v-vi, 1-4, Table 2) (Bundgaard); (Ex. 1011 at 530, 533, 535, 536 and Tables 1 and 2.) (Brynne); (Ex. 1005 at 2:5-10, 1:13-17; 6:4-5; 6:24-28)(Johansson). • "Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency and urge incontinence." Ex. 1011 at 530. • "Preclinical studies have shown that tolterodine has high antimuscarinic potency in guinea pig and human detrusor muscle and displays favorable selectivity for the urinary bladder over salivary glands in vivo." *Id*.

IX. EVEN IF CONSIDERED, SECONDARY CONSIDERATIONS FAIL TO OVERCOME THE EVIDENCE OF OBVIOUSNESS.

The Board has repeatedly held that, at the institution phase, evidence of secondary considerations presented by the Patent Owner should be addressed in a trial where the parties may develop and the Board may consider a full record. *See, e.g., 10X Genomics Inc. v. Univ. of Chicago*, IPR2015–01162, Paper No. 14 at 22 (PTAB Nov. 16, 2015); *Petroleum Geo-Services Inc. v. WesternGeco LLC*,

IPR2014-01477, Paper No. 18 at 32 (PTAB Mar. 17, 2015); *Crocs, Inc. v. Polliwalks, Inc.*, IPR2014-00424, Paper No. 8 at 16 (PTAB Aug. 20, 2014) ("We reiterate ... that such secondary considerations are better considered in the context of a trial when the ultimate determination of obviousness is made."). That is the appropriate course here given that there is no showing of such secondary considerations in the patent itself and any secondary considerations would be "insufficient" to "overcome the strong [case] of obviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Petitioner nonetheless preliminarily addresses alleged secondary considerations that Patent Owner may argue, but reserves the right to respond to any arguments asserted by the Patent Owner in this proceeding.

Commercial Success: Commercial success "is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). Patent Owner must prove that sales resulted from the unique characteristics of the invention, and not economic and commercial factors unrelated to the quality of the patented subject matter. *Applied Materials*, 692 F.3d at 1299-1300. Moreover, "if the commercial success is due to an unclaimed feature of the device," or "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco*, 463 F.3d at 1312; *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011)

(commercial success must stem "from the merits of the claimed invention as opposed to the prior art or other extrinsic factors").

Here, multiple facts confirm there is no commercial success. Patent Owner implemented a substantial marketing campaign to migrate patients from tolterodine to fesoterodine. Ex. 1033 ¶¶ 36-40; Ex. 1048. That alone demonstrates no legally cognizable commercial success can be established. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) ("McNeil had launched a massive marketing and advertising campaign in connection with the launch of the … product, obscuring any nexus that might have existed"). Despite the enormous advertising, the campaign was unsuccessful. Ex. 1033 ¶¶ 36-40; Exs. 1037-38. For example, by 2012, Patent Owner had switched only about 7% of patients to fesoterodine (Ex. 1021), an amount roughly equivalent to the portion of patients who did not metabolize tolterodine well. Ex. 1003 ¶ 147. By 2012, fesoterodine's market share for new patients had only reached 4.5% and it peaked at 5.4% in 2013 (Ex. 1033 ¶ 17), despite Patent Owner's heavy promotion and existing relationships with physicians through sales of Detrol. *Compare Geo M. Martin Co. v. All. Machine Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) (patentee's existing market share "gave it a 'huge advantage' in selling other products" and thus demonstrated lack of nexus).

By contrast to other OAB drugs, Toviaz® performed poorly. Ex. 1033 ¶¶

20-22, 30; Ex. 1038. For example, Myrbetiq® was approved in 2012 and experienced significant commercial success. Ex. 1033 ¶ 22. Indeed, Toviaz® wildly underperformed industry benchmarks. *Id.* ¶ 27; Exs. 1043-44. These comparisons, and the decidedly anemic market share, evidence an absence of commercial success. Lack of nexus for any purported commercial success is unequivocally confirmed given the absence of any price premium for fesoterodine over competing drugs (Ex. 1033 ¶¶ 36-38), the absence of profitability (*id.* ¶¶ 24-28), fesoterodine's consistent failure to meet sales expectations (*id*. ¶¶ 29-30), and the lack of clinical differentiation between fesoterodine and competing drugs. *Id.* ¶¶ 32-35; Ex. 1003 ¶¶ 144-47, Ex. 1021 at 15.

Unexpected Results: Probative evidence of unexpected results "must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers*, 752 F.3d at 977. Moreover, a "'mere difference in degree' is insufficient," and instead a "marked superiority" must be shown. *Id.*

There is nothing unexpected about the results achieved with fesoterodine. Ex. 1003 ¶¶ 140-148. As to efficacy, clinicians have recognized that, even after "[a]n extensive review of the randomized trials that evaluated pharmacologic therapies for OAB," there was "no compelling evidence for differential efficacy

across medications." *Id.* ¶¶ 144-46 (citing Ex. 1021 at 15). Nor are there any material differences in side effects. *Id.* Indeed, clinical and market evidence simply confirmed that skilled persons would have had a reasonable expectation of success in addressing the poor metabolization of tolterodine. *Id.* Finally, even assuming Patent Owner could attempt to show unexpected results due to the different dosing regimens of fesoterodine and tolterodine, the patent claims do not specify a particular dosing regimen (*id*.) and, thus, Patent Owner cannot demonstrate any nexus to the claimed subject matter.

Long Felt Need: Patent Owner would need to document any alleged need and that it was long-felt. It cannot do so. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA Inc*., 752 F.3d 967, 979 (Fed. Cir. 2014) (no long felt need existed where other drugs for hepatitis B were approved before approval by FDA of the patented drug). The patent never claims that the invention meets a long felt need. In 1998, other OAB drugs existed and, at best, any need resided in improving tolterodine effectiveness in the small portion of patients who did not metabolize tolterodine well. Ex. 1003 ¶ 142. But such need was demonstrably not "long felt" as it was identified on the 1998 label for tolterodine. *Tex. Instruments v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem."). Finally, to the extent there was any need to deliver higher

doses of fesoterodine, either in poor or extensive metabolizers, no studies contrast the dosing regiments of tolterodine and fesoterodine (Ex. 1030 ¶ 38; Ex. 1003 ¶¶ 146-147) and nothing in the patent claims addresses dosing levels. *In re Kao*, 639 F.3d at 1068.

X. THE PROPOSED REJECTIONS RAISE NEW ISSUES IN WHICH PETITIONER WILL LIKELY PREVAIL.

This petition must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets and exceeds this threshold. In addition, this Petition addresses issues not previously considered during examination. Except for Johansson (Ex. 1005), none of the references relied upon were cited during examination of the '650 patent. Even as to Johansson, it was cited against original claims 18, 20, 23, and 25 that applicant subsequently canceled. *See* Ex. 1002, August 2003 Rejection and November 2003. Thus, the prosecution history does not address whether a skilled artisan would have found it obvious to modify the known 5-HMT active metabolite to achieve the claimed compound and to formulate it as an acid addition salt for treatment of overactive bladder.

For at least these reasons, Petitioners are reasonably likely to prevail in challenging at least one of challenged claims based on the prior art under 35 U.S.C. § 103. Accordingly, this Petition meets and exceeds the threshold requirements of 35 U.S.C. § 314(a).

Respectfully submitted,

WILEY REIN LLP

By: /Neal Seth, #67,075/
Neal Seth, Reg. No. 67,075

CERTIFICATE OF SERVICE ON PATENT OWNER
UNDER 37 C.F.R. § 42.105(A)

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), the undersigned certifies that, on the 18th day of August 2016, a complete and entire copy of this document was provided to the Patent Owner by mailing a copy of the same via FedEx® to the following attorneys of record for the Patent Owner:

Jeffrey Ginsberg
Kenyon & Kenyon LLP
One Broadway
New York, New York 10004-1007

with a courtesy copy to counsel for Pfizer and UCB Pharma GMBH as follows:

Jack Blumenfeld
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
Wilmington DE 19899

Dimitrios T. Drivas
Jeffrey J. Oelke
James S. Trainor, Jr.
Ryan P. Johnson
Robert Counihan
WHITE & CASE LLP
1155 Avenue of the Americas
New York, NY 10036

/Neal Seth, #67,075/
Neal Seth, Reg. No. 67,075