Drug Regimen Review Center
University of Utah College of Pharmacy

Urinary Antispasmodics: β-3 agonist(s)

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Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) describes overactive bladder (OAB) as having to void or empty the bladder more than 8 times in a day or more than 2-3 times/night (nocturia). This may be associated with the loss of large or small amounts of urine (urge incontinence), but not all patients with OAB experience urinary incontinence. OAB usually results from an involuntary increase in bladder pressure due to bladder smooth muscle (detrusor) over-activity.[1]

Urinary tract infections (UTI), other conditions (e.g. diabetes insipidus), and some other factors (e.g. fluid intake, excessive nighttime urine production) are unrelated to OAB and should be excluded as these may be responsible for similar symptoms. In summary, there are 4 symptom characteristics to OAB; urgency, frequency, nocturia and urgency incontinence (in the absence of UTI, other obvious pathology, or factors).[2]

The major subtypes of urinary incontinence differentiated by etiology are:

1) Bladder overactivity (urge incontinence)
2) Urethral overactivity/bladder underactivity (overflow incontinence)
3) Urethral underactivity (stress incontinence)

Some patients may experience mixed incontinence.

OAB affects 33 million men and women in the United States (17% of American adults); and it is more common in women (9-43% vs. 7-27%)[2] and in older people.[3,4] Urgency, frequency and incontinence has a noticeable negative impact on quality of life with psychological (anxiety and depression) and social consequences (restricted activities).[1] Most patients have symptoms for years and it is common for patients to only seek treatment after an extended period of symptoms.[2]

Management of OAB includes behavioral and non-pharmacological treatment (e.g. bladder training, pelvic floor exercises, and electrical stimulation), or pharmacological treatment.[4] Anticholinergic drugs are the most efficacious agents for the pharmacological treatment of OAB. Anticholinergic drugs can reduce the overactivity of the bladder muscle and the feeling of urgency by inhibiting the muscarinic receptors in the bladder, which causes smooth muscle relaxation.[5] Oxybutynin is an antimuscarinics which has been used for more than 4 decades and it remains the most widely prescribed medication for OAB in the world.[6]

In the past, many patients had insufficient symptom relief or experienced adverse effects to antimuscarinics treatment. After antimuscarinics treatment failure, only invasive treatments (such as botulinum toxin) could be considered as there were no other drugs available. On June 28, 2012 the FDA announced the approval of a new treatment option; Myrbetriq (mirabegron) extended-release tablets for the treatment OAB.[7] It has also been approved in Japan and Europe.[8]

This review will focus on Mirabegron as a treatment option for OAB. A summary of the American Urological Association (AUA) guidelines (May 2012) for the treatment of OAB has been included in this review. The antimuscarinics were discussed in the previous review. This review will not include the other treatment options such as behavioral approaches, neuromodulation therapies, onabotulinumtoxinA, low-dose vaginal estrogen (used to replace declining estrogen in vaginal and urethral tissues of menopausal women with atrophic vaginitis incontinence symptoms)[2], tricyclic antidepressants, and antimuscarinics; or off-label uses of the OAB indicated anticholinergic drugs (such as gastrointestinal disorders).

Management of OAB - Beta-3-adrenoceptor agonist

Mirabegron is the first drug of this new class (β-3 agonist) to be approved by the FDA. It is available as oral once-daily extended-release tablets in 25mg and 50mg dosage strengths and it became available in the fourth quarter of 2012.
Mirabegron is a potent and selective beta-3 adrenoceptor agonist which activates beta-3 adrenoceptors on the detrusor muscle and a triangular region of the bladder called the trigone area, causing relaxation of the bladder to facilitate filling of the bladder and storage of urine (increase bladder capacity with no change in micturition pressure and residual volume).[9-12]

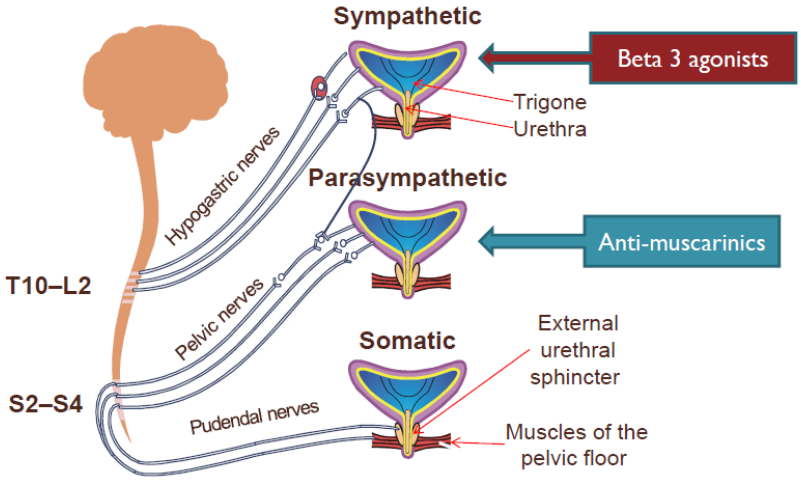

Fig.1 Neurogenic Innervation and Control of Bladder Musculature
(from the FDA meeting slide show)[13]

- Activation of the parasympathetic pathway => detrusor muscle contraction and micturition
- Activation of sympathetic pathway => inhibits detrusor contract ion and contracts the bladder outlet

There are three subtypes of β-adrenoreceptors (β-1, β-2, and β-3) in the detrusor muscle and the urothelium. The β-3 subtype is the most common in the human detrusor and at usual doses, mirabegron is believed to display selectivity for the beta-3 adrenergic receptor subtype compared to its affinity for the beta-1 and -2 adrenoceptor subtypes (showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR).[7,14,15] Results in humans indicate that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg.[15]

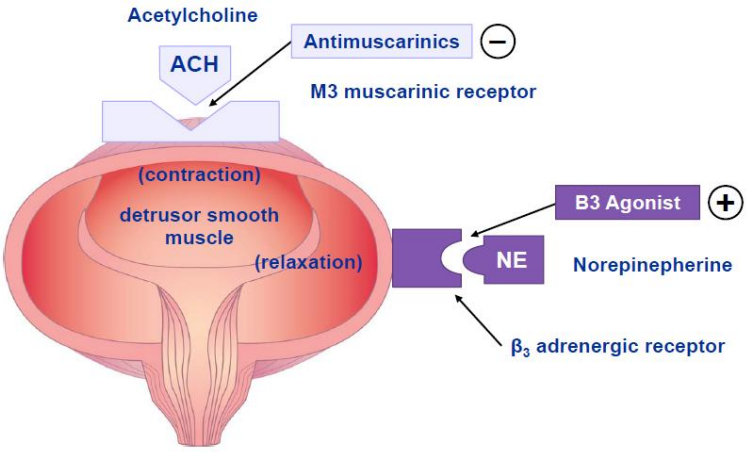

Fig.2 Neurogenic Innervation and Control of Bladder Musculature – receptor sites
(from the FDA meeting slide show)[13]

Other β-3 agonists

Amibegron was the first orally active β-3 agonist, but development was discontinued. It has antidepressant and anxiolytic effects (capable of entering the CNS).[16]

In 2006, Boehringer Ingelheim discontinued development of ritobegron (KUS 7483).[17] In 2012, some in vitro and in vivo (animal) studies on ritobegron were published.[18,19]

Solabegron is currently in clinical development for the treatment of overactive bladder and irritable bowel syndrome (phase 2 study recently published).[20]

How supplied and maximum usual dosage

Table - Usual and Maximum Doses of β-3 agonist(s)[15,21]

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling	Maximal Recommended Dose per Product Labeling
β-3 agonists				
Mirabegron Extended-release (Myrbetriq)	No	Tablets: 25 mg and 50 mg	Starting dose: 25 mg once daily. 25 mg is effective within 8 weeks. May increase dose to 50 mg once daily based on individual efficacy and tolerability. Patients with Severe Renal Impairment or Patients with Moderate Hepatic Impairment: Maximum dose is 25 mg once daily Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment: Not recommended.	Adults: 50 mg

American Urological Association (AUA) Guideline

Mirabegron was not approved by the FDA at the time the AUA guideline was prepared and published.
The only mention to this new class in the report is the following paragraph:
"Recently, β3-agonist class of medications (i.e., mirabegron) has shown promise in OAB treatment. These lines of research focus on the bladder and present a unique opportunity to advance bladder-targeted diagnostics and therapeutics."[3]

This guideline was written by the Overactive Bladder Guidelines Panel of the American Urological Association Education and Research, Inc. and included urologists and other clinicians with specific expertise on this disorder. It was funded by the AUA and the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction and committee members received no remuneration for their work.
"This guideline's purpose is to provide direction to clinicians and patients regarding how to recognize non-neurogenic overactive bladder (OAB), conduct a valid diagnostic process and approach treatment with the goals of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden."[2] It was not intended to be interpreted rigidly and an individualized approach for a particular patient is suggested as the most effective approach.

Reference documents for review

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline (2012)

- http://www.auanet.org/content/media/OAB_guideline.pdf

Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Algorithm (2012)

- http://www.auanet.org/content/media/OAB_algorithm.pdf

Sources of evidence for guideline (for majority of treatment portion):

- Primary source: Systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment Number 187 titled Treatment of Overactive Bladder in Women (2009)[22] (literature search: Jan 1966 – Oct 2011)
- Additional literature searches by AUA (for treatments not covered and articles published between Oct 2008 and Dec 2011)
- All these studies (including those excluded in the primary source) were added to the database and the AUA performed its own qualitative and quantitative analyses of the extracted data including meta-analyses as appropriate

A summary of recommendations for the treatment portion of the guideline that involves urinary antimuscarinics was included in the previous report.

National Institute for Health and Care Excellence (NICE) Guidance

A NICE technology appraisal (Mirabegron for adults with symptoms of overactive bladder) is due in June 2013.

Appraisal Committee's preliminary recommendations:

http://guidance.nice.org.uk/TA/Wave0/667/Consultation/DraftGuidance

"1.1 Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.

1.2 People currently receiving mirabegron whose condition does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop."[23]

Clinical Efficacy - Randomized Controlled Trial(s)

Mirabegron's safety and efficacy in patients with OAB were evaluated in global 12-week (3 month) phase IIb and phase III studies and one 12-month study (TAURUS).[11,12] Appendix 1 (table 5) contains a summary of mirabegron trials.

Study	Control
178-CL-047 (ARIES)[24]	Placebo
178-CL-074 (CAPRICORN)[25]	Placebo
178-CL-046 (SCORPIO)[26]	Placebo & active - tolterodine
178-CL-049 (TAURUS)[27]	Active - tolterodine

According to the FDA, efficacy of mirabegron was demonstrated in three randomized controlled trials (ARIES; CAPRICORN; and SCORPIO) using composite endpoints of (1) change from baseline in the mean number of incontinence episodes per 24 hours and (2) mean change from baseline in the mean number of micturitions per 24 hours. The change from baseline to end of treatment (Week 12) in mean volume voided per micturition (secondary endpoint) was also reviewed. [25]

Mirabegron 50 mg met the primary and secondary endpoints in phase 3 studies and it has been demonstrated to be clinically superior to mirabegron 25 mg. Mirabegron 25 mg was included in the CAPRICORN study (178-CL-074) and it met the primary endpoint, but not the key secondary endpoint.[25]

Primary efficacy analysis for mirabegron 50 mg – pooled efficacy analysis:

1) Reduction in incontinence episodes vs. placebo = -0.40 ($p<0.001$ corrected for multiplicity)
2) Reduction of micturitions per 24 hours vs. placebo = -0.75 ($p<0.001$ corrected for multiplicity)

The TAURUS 1 year active controlled study also showed efficacy for mirabegron 50 mg over the course of the study period using the co-primary endpoint assessment above.
After analysis, both mirabegron 25 mg and 50 mg was efficacious compared to placebo (statistically significant reductions in the primary endpoints).[25]

Table 2 - Subpopulation efficacy analyses adapted from the FDA background document and mirabegron product label[15,25]

Gender	The Cmax and AUC of mirabegron were approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20% to 30% higher in females compared to males. The product label states that no dose adjustment is necessary based on gender.
Age	It appears that there is an increased efficacy in subjects >65 yeast of age as compared to subjects <65 years of age (number of incontinence episodes per 24 hours adjusted mean vs. placebo: 50mg -0.66 vs. -0.22; 25 mg -0.59 vs. -0.29)
Body Mass Index (BMI)	No significant difference for any BMI group.
Race	Too few subjects in non-white categories to allow further analysis.
Diabetics	The FDA report stated that data suggest that mirabegron 50 mg is not associated with glucose dysregulation.
Concomitant alpha-blocker use	The number of subjects using alpha-blockers was too small to draw meaningful conclusions.
Concomitant B-blocker use	According to the FDA report, it appears that subjects using beta-blockers have similar efficacy results compared to subjects not on ongoing beta-blockers.
Concomitant benign prostatic hyperplasia (BPH)	There were too few men with BPH to draw meaningful conclusions. However, the 50 and 100 mg was not effective in decreasing the mean number of incontinence episodes in men with BPH.
Concomitant diuretic use	Efficacy results for patients on diuretics and 50 or 100 mg mirabegron exceeded results for the overall study population for the primary efficacy endpoints.

The NICE Appraisal Committee concluded that mirabegron was clinically effective with modest improvements compared with placebo (like antimuscarinics), but equivalent efficacy to all antimuscarinics is uncertain.[23] All three RCTs (ARIES; CAPRICORN; and SCORPIO) evaluated the clinical effectiveness of mirabegron versus placebo, and the SCORPIO trial included an active control of tolterodine, but the manufacturer chose not to present this comparison data (vs. tolterodine) as it was not powered to evaluate the

superiority or non-inferiority of mirabegron versus tolterodine (according to the manufacturer none of the studies that included an active control arm of tolterodine was powered to detect this).[12]

NICE lists comparators of interest as oxybutynin (including modified-release preparations; also non-oral), tolterodine, fesoterodine, solifenacin, and trospium; and comparative studies for mirabegron with these are needed to fully address the decision problem.[12]

Population	Intervention	Comparison	Outcome
Adults with OAB Sub-groups: men and women; previously untreated and previously treated OAB	Mirabegron	placebo & anticholinergics: oxybutynin (including modified-release preparations; also non-oral), tolterodine, fesoterodine, solifenacin, and trospium	urinary frequency; frequency of urge urinary incontinence; symptoms of urgency; nocturia; adverse effects of treatments; HRQoL

The populations in these studies are likely to be representative of the population in Utah as the studies were multicenter and multinational studies (apart from the 2 multicenter studies in Japan).
The Appraisal Committee for NICE considered the relevant subgroups (men and women; pre-treated or treatment-naïve) and also concluded that there was no evidence for differential clinical effectiveness.[23]

Safety and adverse effects

- Phase 2 or 3 studies: 8752 subjects
- Phase 1 studies: 1800 volunteers

} 7325 participants received mirabegron[25]

Phase 2/3 Population that received the formulation submitted to the FDA (to be marketed): **4414 subjects**[25]	2142 placebo
	811 mirabegron 25 mg
	2131 mirabegron 50 mg
	1305 mirabegron 100mg
	167 mirabegron 200 mg
	958 tolterodine ER 4 mg

Mirabegron is a strong agonist selective for β(3) adrenoceptors (compared to β(1)- and β(2)-adrenoceptors) and limited effects on other organ systems are expected, but more clinical and long-term studies are needed especially with regards to effects on the cardiovascular system, pharmacokinetic interactions with other drugs, and increased incidence of new malignant events.[11,28] In clinical trials, the reported incidence and severity of adverse effects were similar to antimuscarinics, but with a lower incidence of dry mouth compared to tolterodine.[11,15] Key safety concerns for mirabegron identified by the FDA included cardiovascular safety (effects on blood pressure, heart rate, and cardiovascular AEs), neoplasms, hepatic safety, urinary tract related AEs, hypersensitivity reactions, and spontaneous pregnancies.[25] There were 11 deaths in the entire mirabegron development program and none of these appear directly related to treatment with mirabegron.[25]

Adverse effect information was collected from the SCORPIO, ARIES, and CAPRICORN trials, but the TAURUS long-term follow-up study (12 months) was the main study investigating adverse effects of mirabegron treatment. Participants in TAURUS were recruited from SCORPIO and ARIES which may therefore be a selected rather than a representative OAB population.[23]

Table 3 - Key safety issue concerns [11,25]		
Phase 1 studies	**Phase 3 studies**	**Implication**
Elevation in blood pressure of approximately 3-4 mmHg was observed at T_{max} 50 mg and 200 mg: larger increases in heart rate - 4.0 to 4.1 and 10.3 to 11.8 bpm, respectively, at one or more time points.	Elevation in systolic and diastolic blood pressures was only approximately 1 mmHg 50 mg once daily: approximately 1 bpm increase in adjusted mean change from baseline pulse compared to placebo	FDA: potential **cardiovascular** safety signal (reasons for discrepancies and the extent and clinical relevance are not completely clear) Global OAB safety database: relative risk (RR) of major adverse cardiovascular risk events was 0.24 [95%CI, 0.02 to 1.69]. The hypertension treatment emergent adverse effects (TEAEs) & serious adverse effects (SAEs) were similar for mirabegron, placebo and tolterodine in the long-term study, but there are concerns over the increases seen in phase 1&3 studies. It is unlikely that mirabegron causes atrial fibrillation (small incidences, small differences between groups, and alternative explanations). Pivotal studies and a dedicated large QT study (178-CL-037) demonstrated the absence of a clinically meaningful QT prolongation at mirabegron 50 mg and 100 mg doses.
-	Increased incidence of a variety of **neoplasms** in mirabegron 100 mg group (1.3%) compared with 50 mg (0.1%) and tolterodine (0.5%).	Unknown whether these data represent a true mirabegron-related effect (could have preexisted treatment).
CYP2D6 moderate inhibition		Potential for pharmacokinetic interaction with other drugs that are CYP2D6 substrates
There were reports of liver function test elevations and three reports of severe hepatotoxicity		FDA: It appears that mirabegron may in some subjects cause **hepatotoxicity**.
-	Phase 3 Population: ≥1 UTI TEAEs was reported by 99/2736 (3.6%) mirabegron subjects (Vs. 34/1380 (2.5%) placebo; 15/495(3.0%) tolterodine subjects)	FDA: There appears to be a modestly increased incidence of **UTI** in mirabegron subjects as compared to placebo. Rare potential for urinary tract related adverse events (urinary tract infection, acute urinary retention, and renal colic) may be related to infrequently increasing post-void residual urine.
Urolithiasis: There appears to be an increased incidence of reported nephrolithiasis in mirabegron subjects		FDA: It is not known if these were diagnosed incidentally or secondary to symptoms. Proteinaceous bladder calculus was noted at very high mirabegron doses in preclinical studies, but no renal calculi were noted.
No cases of anaphylaxis or angioedema reported, but 29 reports of non-immediate hypersensitivity (vs. 1 in placebo and 3 in tolterodine); 1 immediate hypersensitivity reaction in a 100 mg mirabegron subject (pruritis). 7 severe: (2 cases of erythema multiforme [post marketing-Japan], (1) Stevens Johnson Syndrome, 2 cases of leukocytoclastic vasculitis, (1) hemolytic anemia and (1) possible autoimmune hepatitis).		FDA: Mirabegron appears associated with the occurrence of clinically significant **hypersensitivity reactions**, some of them severe.
Isolated reports of glaucoma and increases **intraocular pressure** during clinical trials.		Concerns were addressed through a dedicated ocular safety study (310 healthy volunteers): Mirabegron did not appear to increase intraocular pressure

Table 4: Percentage of patients with adverse reactions
(adapted from table 1&2 of the Myrbetriq product label)[15]

	Studies 1,2,3: Adverse events exceeding placebo rate and reported by ≥1% of patients			Study 4: Adverse events reported by ≥2% of patients	
	Placebo (%)	**Myrbetriq 25 mg (%)**	**Myrbetriq 50 mg (%)**	**Active control (%)**	**Myrbetriq 50 mg (%)**
Number of patients	**1380**	**432**	**1375**	**812**	**812**
Hypertension	7.6	11.3	7.5	9.6	9.2
Tachycardia	0.6	1.6	1.2	-	-
Headache	3	2.1	3.2	2.5	4.1
Urinary tract infection	1.8	4.2	2.9	6.4	5.9
Cystitis	-	-	-	2.3	2.1
Abdominal pain	0.7	1.4	0.6	-	-
Constipation	1.4	1.6	1.6	2.7	2.8
Diarrhea	1.3	1.2	1.5	-	-
Upper respiratory tract infection	1.7	2.1	1.5	-	-
Nasopharyngitis	2.5	3.5	3.9	3.1	3.9
Sinusitis	-	-	-	1.5	2.7
Influenza	-	-	-	3.4	2.6
Arthralgia	1.1	1.6	1.3	2	2.1
Back Pain	-	-	-	1.6	2.8
Fatigue	1	1.4	1.2	-	-
Dizziness	-	-	-	2.6	2.7
Dry mouth	-	-	-	8.6	2.8

The most commonly reported adverse reactions for Studies1-3 (SCORPIO, ARIES, and CAPRICORN) and study 4 (TAURUS) (> 2% of Myrbetriq patients and > placebo) include[15]:

- Hypertension
- Urinary tract infections
- Nasopharyngitis
- Headache

Multiple intrinsic factors have been examined and no dose adjustments are necessary based on age, gender, race, and polymorphism for CYP2D6. A dose adjustment to 25 mg is recommended in severe renal and moderate hepatic impairment (not studied and not recommended in end-stage renal disease and severe hepatic impairment). With regards to extrinsic factors, there is a limited potential for drug-drug interactions with drugs metabolized by CYP2D6 and a dose adjustment may be necessary for narrow therapeutic index drugs. [13]

Contraindications
No specific contraindications have been determined.[15]

Special populations
The safety and efficacy of mirabegron have not been established in pediatric patients (the studies did not include <18 year old patients). No dose adjustment is recommended for elderly patients. It is not recommended for use by nursing mothers and should only be used in pregnancy if the benefit to the mother outweighs the potential risk to the fetus (Category C).[15]

Warnings and precautions
Myrbetriq can increase blood pressure and periodic blood pressure determinations are recommended, especially in hypertensive patients. It is not recommended for use in severe uncontrolled hypertensive patients.

Myrbetriq should be administered with caution in patients with urinary retention or bladder outlet obstruction and in patients taking antimuscarinics for OAB because of risk of urinary retention.[15]

The FDA report stated that the risk of acute urinary retention with mirabegron in short-term studies appears small and the long term use of mirabegron was associated with a small incidence of urinary retention.[25]

Interactions
Myrbetriq is a moderate inhibitor of CYP2D6 and appropriate monitoring is recommended for patients taking drugs metabolized by CYP2D6; dose adjustment may be necessary for *narrow therapeutic index CYP2D6 substrates*. The product label recommends that the lowest dose of digoxin be prescribed when initiating a combination of Myrbetriq and *digoxin* and to monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect.[15]

- **Please refer to the product labeling for complete prescribing information.**

Adverse reaction rates observed in clinical trials may not reflect the rates observed in clinical practice due to varying conditions and postmarketing reports will therefore contain useful additional insight into mirabegron's safety profile.

Utah Medicaid Utilization Data

As this is a new medication (and new class), there is currently no Utah Medicaid utilization data available as of April 29, 2013.

Conclusion

According to the AUA OAB guidelines, behavioral therapies should be first-line and may be combined with antimuscarinics. Antimuscarinics should be offered as second-line treatment. "No treatment is an acceptable choice made by some patients and caregivers."[2]

Efficacy of mirabegron compared to placebo was demonstrated in randomized controlled trials. [25]

A total of 7325 subjects received mirabegron in the clinical development program. There were 11 deaths which appear unlikely to be related to mirabegron treatment, and the incidence of Serious Adverse Events (SAEs) in the studies was low and comparable between placebo, mirabegron and tolterodine groups. In the 12-Week OAB Phase 3 population, Treatment Emergent Adverse Events (TEAEs) leading to permanent discontinuation were infrequent; the most common AEs leading to discontinuation were constipation, headache, and hypertension; and the TEAEs reported by ≥3.0% of subjects were hypertension, nasopharyngitis and UTIs. According to the FDA, the routinely collected data do not appear to indicate serious risks of mirabegron, but some safety concerns exist with regards to increases in heart rate and blood pressure, liver function test abnormalities, urinary tract related AEs, neoplasms, and hypersensitivity reactions.[25]

β_3-AR agonists may be a promising alternative to antimuscarinics in the treatment of OAB especially in those who cannot tolerate the specific side effects of antimuscarinics (particularly dry mouth), but clinical trial efficacy does not always translate into real world effectiveness. Patients in the trials were actively encouraged to continue taking the drug for the entire trial duration and data were therefore unlikely to be representative of persistence rates in clinical practice.[23] Therefore, real-life long-term information in terms of efficacy, safety, and tolerability is needed to determine its place in therapy. There have been no published trials directly comparing mirabegron with current therapies. Mirabegron appears to offer a treatment option of similar efficacy to current antimuscarinic therapies (equivalency to all antimuscarinics are uncertain) with less dry mouth (compared to tolterodine) and a different side effect profile (not necessarily better).[23]

The American Pharmacist Association update on Myrbetriq states that overall, it is a welcome addition for the management of OAB especially since many patients discontinue treatment due to adverse effects to antimuscarinics.[29] However, the update also states that the risk–benefit profile of mirabegron must be considered and account for the difference in cost compared to currently available generic antimuscarinics. Special mention of the unknown long-term cardiovascular safety is made and that some clinicians may therefore choose to use this agent cautiously in patients with known heart and vascular problems. Examples of patients that may benefit from this new class include older patients (experience more dry mouth) and patients with Alzheimer disease.[29] These patients are at increased risk for the cognitive effects to antimuscarinics and anti-muscarinic agents are included in the Beer's Criteria for potentially inappropriate use in older patients.[30] Drug-interactions between the anticholinergics (for OAB) with cholinergic agents that are used to manage Alzheimer disease is another problem in these patients.

The preliminary recommendation of a NICE technology appraisal due in June 2013 (Mirabegron for adults with symptoms of overactive bladder) is that mirabegron is an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects.[23]

Appendix 1 – Table 5 Summary of trials

Author(s)	Title	Date of publication	Type of study	n	Method	Primary outcomes	Results
Three pivotal large-scale phase III studies conducted by Astellas (considered for the efficacy analysis in the report of the Division of Reproductive and Urologic Products of FDA)							
Khullar et al.[26]	Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. **178-CL-046**	2013	European–Australian multicenter, randomized, double-blind, parallel-group, placebo and active controlled phase III trial (**SCORPIO trial**)	1987	2-week placebo run-in period, then were randomized to receive one of the following once daily for 12 weeks: **placebo** (n = 494), mirabegron 50 mg (n = 493), mirabegron 100 mg (n = 496), or **tolterodine** SR 4 mg (n = 495).	Urinary frequency; Incontinence frequency	Statistically significant decrease from baseline [95% confidence intervals) in mean number of micturitions with 50 mg & 100 mg mirabegron (−1.93 [-2.15 to -1.72] and −1.77 [-1.99 to -1.56] respectively vs. placebo -1.34 [-1.55 to -1.12]) and mean number of incontinence episodes per 24 hours (−1.57, −1.46, respectively) compared with placebo (-0.17). Secondary endpoint - significant change from baseline Volume Voided (mL) per Micturition: 24.2 for mirabegron 50 mg (compared to placebo)
Nitti et al.[24]	Results of a Randomized Phase III Trial of Mirabegron in Patients with Overactive Bladder. **178-CL-047**	2013	North American multicenter (US & Canada), randomized, double-blind, parallel-group, placebo-controlled phase III trial (the **ARIES trial**)	1329	2-week placebo run-in period, then randomly assigned patients to three treatment arms: **placebo**, mirabegron 50 mg and mirabegron 100 mg for 12 weeks.	Urinary frequency; Incontinence frequency	Statistically significant reductions from baseline were observed with 50 mg and 100 mg mirabegron in the number of incontinence episodes (−1.47[-1.69 to -1.25], and −1.63[-1.86 to -1.40] vs. placebo (−1.13[-1.35 to -0.91], and in the number of micturitions per 24 h (−1.66[-1.92 to -1.40], and −1.75[-2.01 to -1.48] vs. placebo (-1.05[-1.31 to -0.79). Secondary endpoint - significant change from baseline Volume Voided (mL) per Micturition: 18.2 for mirabegron 50 mg (compared to placebo)

FDA (2012) Summary of safety and efficacy as basis for Advisory Committee briefing document.[25]	To assess the efficacy and safety of the beta-3 agonist mirabegron (25 mg qd and 50 mg qd) in subjects with symptoms of overactive bladder. **178-CL-074**	Data on file 2010 report	European–North American (Europe, US and Canada), randomized, double-blind, placebo-controlled phase III trial (the 178-CL-074 **CAPRICORN** trial)	1306	Comparing mirabegron 25 mg and 50 mg with **placebo**.	Urinary frequency; Incontinence frequency	Results of this trial are still unpublished (submitted to FDA by Astellas) Statistically significant reductions from baseline were observed with both doses of mirabegron in the number of incontinence episodes (−0.96, −1.36, and −1.38 for placebo, mirabegron 25 mg, and 50 mg, respectively; $p < 0.05$) and in the number of micturitions per 24 h (−1.18, − 1.65, and −1.60 for placebo, mirabegron 25 mg, and 50 mg, respectively; $p < 0.05$). Secondary endpoint - significant change from baseline Volume Voided (mL) per Micturition: 20.7 for mirabegron 50mg (compared to placebo)
Long-term study							
Chapple et al.[27]	Randomised, double-blind, active-controlled phase III study to assess the long-term safety and efficacy of mirabegron in overactive bladder (OAB). **178-CL-049**	2013	Multinational (USA, Europe, Australia, Canada, South Africa) randomized, double-blind, parallel group, active-controlled, phase III trial (the **TAURUS** trial)	2452	Single-blind placebo run-in period of 2 weeks (not designed to demonstrate a statistically significant difference in efficacy), then randomized to study groups for **12 months** (mirabegron 50 mg and 100 mg and **tolterodine** SR 4 mg)	Incidence and severity of treatment-emergent adverse event (TEAE)	Both doses: improvements in OAB symptoms were observed by month 1, with continued improvement until at least month 3 and maintenance of the effect through month 12, as measured by the change from baseline for mean number of micturitions per 24 h, mean number of incontinence episodes per 24 h, and improvements in mean volume voided/micturition.
Other studies							
BMJ STA report[12]	A Phase 2, double-blind, placebo-controlled, parallel group study of YM178 in patients with overactive bladder. **178-CL-045**	Data on file 2010 report	Phase II RCT, double-blind, multicenter (Japan) **178-CL-045**	842	Mirabegron 25 mg, 50 mg, 100 mg, placebo, 12 weeks	Urinary frequency	Data on file Not included in report data table

Chapple et al.[31]	Dose-ranging study of once- daily mirabegron (YM178), a novel selective 3-adrenoceptor agonist, in patients with overactive bladder (OAB) **178-CL-044**	2010	European dose-ranging phase IIb trial, RCT, double-blind, multicenter (**DRAGON trial**)	928	**Placebo,** once-daily mirabegron 25 mg, 50 mg, 100 mg, and 200 mg, **tolterodine ER 4 mg**	Urinary frequency	Statistically significant dose-dependent reduction in mean micturition frequency with 50, 100, and 200 mg of mirabegron compared with placebo (−2.1, −2.1, and −2.2 respectively; $p < 0.05$). Also, significantly increased mean volume voided per micturition (dose-dependent effect), decreased the mean number of incontinence episodes, urgency incontinence episodes, and urgency episodes per 24 h (compared to placebo).
BMJ STA report[12]	Phase III Study of YM178, a double-blind group comparison study in patients with overactive bladder. **178-CL-048**	Data on file 2010 report	Phase III, RCT, double-blind, multicenter (Japan) **178-CL-048**	1139	Mirabegron 50 mg, tolterodine tartrate 4 mg, placebo, 12 weeks	Urinary frequency	Data on file Not included in report data table
Phase 11a (PD, safety, tolerability, PK)							
Chapple et al.[32]	Clinical proof of concept study (Blossom) shows novel B-3 adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. **178-CL-008**	2008b	Randomized, double-blind, parallel group, phase IIa dose-ranging trial (**BLOSSOM trial**) (31 sites in 6 European countries)	262	2-week placebo run-in period, then randomly assigned to four study groups: **placebo** (n = 66), mirabegron 100 mg twice daily (n=65), mirabegron 150 mg twice daily (n=65), and **tolterodine** 4 mg four times daily (n=64) for a *4-week period*.	Urinary frequency; Incontinence frequency	Statistically significant reduction from baseline in mean micturition frequency with 100 and 150 mg of mirabegron (−17% and −18% respectively) compared with placebo (−9%) and tolterodine (−11%). Also, significantly superior to placebo with regard to mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, and urgency episodes per 24 h.

Unpublished							
ClinicalTrials.gov NCT01340027[33]	A study to evaluate the efficacy, safety and tolerability of 6 dose combinations of solifenacin succinate and mirabegron compared to mirabegron and solifenacin succinate monotherapies in the treatment of overactive bladder.	-	Phase II trial, Randomized, Double-Blind, Factorial, Parallel-Group, Active and Placebo-Controlled, Multicenter Dose-Ranging Study **178-CL-100**	2092	Evaluating mirabegron and solifenacin alone and in combination for treating OAB; Solifenacin succinate and Mirabegron Mirabegron Solifenacin succinate Placebo 12 weeks	Change from baseline in mean volume voided per micturition	Study completed (June 2012); no results or publications yet
Studies 178-CL-003, 178-CL-004 and 178-CL-060 were not OAB Studies and were therefore not included in the Global OAB Phase 2/3 Population[34]							
Background Document for Meeting of Advisory Committee for Reproductive Health Drugs April 5th, 2012[25]	178-CL-003	-	Phase 2a, Placebo controlled, dose titration study Poland	59 adults with type 2 diabetes	4-week single-blind placebo run-in followed by 12-week double-blind treatment period. Mirabegron IR 60, 130, 200 mg tablet matching placebo po; once daily after breakfast	Dose titration study	Not included in report data table
Background Document for Meeting of Advisory Committee for Reproductive Health Drugs April 5th, 2012[25]	178-CL-004 Poland	-	Phase 2a, Placebo controlled, dose titration study Poland	60 adults with Type 2 diabetes on stable metformin monotherapy	4-week single-blind placebo run-in followed by 12-week double blind treatment period. Mirabegron IR 60, 130, 200 mg tablet matching placebo po; once daily after breakfast Metformin 500 & 850 mg tablets po	Dose titration study	Not included in report data table
Background Document for Meeting of Advisory Committee for Reproductive Health Drugs April 5th, 2012[252525]	178-CL-060	-	Phase 2a, Placebo controlled, dose titration study Canada and US	200 men with LUTS (lower urinary tract symptoms) and BOO (bladder outlet obstruction)	12-week DB treatment period. Mirabegron IR 60, 130, 200 mg tablet matching placebo po; once daily after breakfast	Dose titration study	Not included in report data table

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