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Abbreviated Class Update: Overactive Bladder

Month/Year of Review: January 2013
PDL Class: Genitourinary – Overactive Bladder
New drug: Mirabegron (Myrbetriq™)
End date of literature search: September 2012

Date of Last Review: 2006
Source Document: DERP Report
Manufacturer: Astellas Pharma Technologies, Inc.

Current Status of PDL Class:

- Preferred Agents: Fesotodine Fumarate (Toviaz®), hyoscyamine drops/elixir, hyoscyamine ER tablets, oxybutynin tablets/syrup, oxybutynin patch (Oxytrol®), oxybutynin ER tablets, and tolterodine (Detrol®)
- Non Preferred Agents: Darifenacin (Enablex®), flavoxate (Urispas®), solifenacin (Vesicare®), tolterodine ER (Detrol LA®), trospium (Sanctura®), trospium ER (Sanctura XR®), and oxybutynin Gel packet (Gelnique®)

Research Questions:

- Is there any new relevant evidence from high quality systematic reviews or evidence-based guidelines demonstrating differences in efficacy or safety between anticholinergic drugs, suggesting recommended changes to the current management of the Overactive Bladder (OAB) class?
- Is mirabegron more effective and/or safer than currently available agents?
- Are there subgroups of patients where mirabegron may be more effective or safer than currently available agents?

Conclusions:

- There is no consistent new evidence from available systematic reviews to change the previous conclusions, and no strong evidence to distinguish between agents in efficacy or adverse events.
- There is low quality evidence that comparisons of extended-release and immediate release formulations tended to find higher rates of adverse events, particularly dry mouth, with immediate release formulations, however no differences in discontinuation rates were found.
- There is low-moderate quality of evidence, based on limited published data, that mirabegron improves short term efficacy outcomes including change in mean number of incontinence episodes and micturitions in 24 hours, compared to placebo and is generally well tolerated. Data came from two short term (12 week) published trials (one good quality; one fair quality).
- There is insufficient direct evidence comparing mirabegron to other agents for the treatment of OAB.

Recommendations:

- Due to the lack of long term clinical outcome data and direct comparative data suggesting superior efficacy or tolerability of mirabegron over currently available agents, make mirabegron a non-preferred agent.

Previous HRC Conclusions:

- There is no available data on flavoxate.
- There is insufficient evidence to distinguish difference in efficacy or adverse events between available agents
- There is no consistent evidence of an advantage for extended release formulations.

Reason for Review:

In 2006, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the overactive bladder drugs. Since this review, in 2009 the Oregon Evidence-based Practice Center (EPC) Drug Effectiveness Review Project (DERP) completed an updated report for the drug class review. In addition, in June 2012, mirabegron was approved by the FDA for the treatment of overactive bladder. It is the first oral overactive bladder treatment with a distinct mechanism of action since the launch of anticholinergics 30 years ago. This update will examine the place in therapy for mirabegron, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

The International Continence Society defines OAB as urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia, in the absence of pathologic or metabolic factors that would explain these symptoms[2]. Overactive bladder is characterized by the presence of involuntary bladder contractions that occur during bladder filling despite the patient's attempt to suppress them. Bladder contraction is mediated via cholinergic muscarinic receptors in bladder smooth muscle. The most common cause of overactive bladder syndrome is detrusor overactivity. It is a common disabling condition that affects health-related quality of life.[3]

While urge incontinence is not inevitable, its incidence does increase with age. Epidemiological studies of men and women from North America have reported a prevalence of OAB of 16.0% and 16.9%, respectively[4]. In women, prevalence of urge incontinence increased with age from 2.0% to 19% with a marked increase after 44 years of age, and in men, increased with age from 0.3% to 8.9% with a marked increase after 64 years of age. Among all age groups, OAB without urge continence was more common in men than in women.[4]

Before the treatment of overactive bladder syndrome, a clear diagnosis must be made. Anticholinergics are the main pharmacologic treatments for over active bladder. Anticholinergics work as competitive muscarinic receptor antagonists causing the detrusor muscle to relax and thus reduce the frequency and intensity of contractions of the bladder. Anticholinergic agents have been included in a number of reviews of drugs with high risk of adverse effects in the elderly. These medications reduce symptoms but also can commonly have non-life-threatening side effects such as dry mouth, constipation, dry or itchy eyes, blurred vision, dyspepsia, UTI, urinary retention and impaired cognitive function. The new FDA approved drug mirabegron has a novel mechanism of action that works by stimulating the beta 3-adrenergic receptors in the detrusor muscle of the bladder, causing relaxation of the bladder muscle during the storage phase of the micturition (urination) cycle. It is theorized that due to lack of direct anticholinergic effects, common adverse events associated with anticholinergics, such as dry mouth, constipation, will be avoided. Clinically appropriate measures of effectiveness include change in mean number of incontinence episodes or micturitions per 24 hours, subjective patient assessments of symptoms, and quality of life.

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Methods:
A Medline (Ovid) literature search was conducted since the end of the literature included in the DERP report for new randomized controlled trials (RCT's) and controlled clinical trials comparing medications head-to-head in the treatment of overactive bladder using all included drugs and limits for humans, English language. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Drug Effectiveness Review Project (DERP); 2009[1]
No effectiveness trials were found and the included trials assessed efficacy outcome measures and were short (-12 weeks). Most of the trials were of fair internal validity, but their applicability to community practice was difficult to determine, as the studies generally excluded patients who would have been at risk of serious adverse events from anticholinergic drugs.

Comparative efficacy (Fair quality of evidence)
• When extended-release and immediate-release formulations of the same drug were compared, no differences in efficacy were found.
• Comparisons of different drugs in extended-release and immediate-release formulations more often found the extended-release drug to be superior, but not in all cases.
• No difference among immediate-release products was found.
• For oxybutynin extended-release compared with tolterodine extended-release the better of 2 studies found them equal.

Adverse events
• In longer-term observational studies, poor quality of evidence demonstrated dry mouth was the most common adverse event for all the drugs, with similar rates between drugs. One comparative study found a higher rate and earlier withdrawal with oxybutynin compared to tolterodine, but rates for both drugs were high.
• Short-term trials (fair quality evidence) making direct comparisons indicate a higher incidence of adverse events overall and specifically dry mouth with oxybutynin than with the other drugs. Differences in adverse event profiles between long-acting products and short-acting products are unclear.

Subpopulations
• Evidence from 5 studies was not consistent in identifying differences between men and women in response to tolterodine (poor quality evidence).

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• Older patients were found to respond to oxybutynin, tolterodine extended-release, darifenacin, or solifenacin in post hoc subgroup analyses. Adverse event profiles were similar to those found in the overall trial populations (fair quality evidence).
• Oxybutynin immediate-release and tolterodine immediate-release resulted response and adverse event rates that were similar for Chinese women and for primarily white populations of other studies. Solifenacin was found to have response and adverse event rates in a Hispanic subgroup that were similar to those of the overall trial population in 1 study. Tolterodine extended-release and tolterodine immediate-release were found to be similarly effective in Japanese and Korean women, with fewer adverse events in the tolterodine extended-release group. The Japanese patients were shown to have improved quality of life in both groups; no such analysis was undertaken for the Korean patients.

Flavoxate, scopolamine, and hyoscyamine
• Head-to-head comparisons with flavoxate were poor quality and there were no head-to-head comparisons of scopolamine, or hyoscyamine to another drug for OAB.

Cochrane Collaboration
In March 2012, a Cochrane Review by Madhuvrata P et al. was conducted to compare and determine the differential effects of anticholinergic drugs in the treatment of overactive bladder[5]. The review included 86 trials that compared different anticholinergic drugs for overactive bladder symptoms. In the studies that compared oxybutynin and tolterodine, no statistically significant difference was demonstrated in quality of life (standardized mean difference [SMD] -0.00, 95%CI -0.18 to 0.18; 3 trials), proportion of people reporting cure or improvement (RR 1.01, 95%CI 0.93 to 1.11; 5 trials), or leakage episodes per 24 hours (weighted mean difference [WMD] 0.08, 95% -0.16 to 0.31; 7 trials). Eight trials reported withdrawals due to adverse events and found fewer withdrawals in patients taking tolterodine compared to oxybutynin (6% vs. 12.5%, RR 0.52,95% 0.40 to 0.66) at 8-12 weeks. Dry mouth was the most frequently reported side effect and those taking tolterodine experienced dry mouth statistically significantly less frequently compared to participants taking oxybutynin (RR 0.65, 95% CI 0.60 to 0.71).

Five studies were included that compared trospium versus oxybutynin. No statistically significant difference between groups on reported cure or improvement was found (RR 1.00, 95%CI 0.90 to 1.11; 2 trials) and fewer withdrawals due to adverse events occurred in the trospium group compared to oxybutynin (RR 0.66, 95%CI 0.48 to 0.91; 3 trials). In the two trials that compared propanthelin IR versus oxybutynin IR, there was a statistically significant difference in proportion of patients reporting cure or improvement in favor of oxybutynin (RR 0.71, 95%CI 0.53 to 0.96), but no significant difference in withdrawals due to adverse events (RR 1.43, 95%CI 0.53 to 3.89).).

Five trials were included that compared solifenacin to tolterodine. A statistically significant better quality of life was demonstrated (SMD -0.12, 95% CI 0.23 to -0.01, 4 trials), a statistically significant better cure or improvement (RR 1.25, 95%CI 1.13 to 1.39; 2 trials) and fewer leakage episodes (WMD -0.30, 95%CI -0.53 to -0.08) with solifenacin compared to tolterodine. However, there was no statistically significant difference between withdrawals due to adverse events (RR 1.27, 95%CI 0.84 to 2.23; 5 trials) or dry mouth (RR 1.04, 95% CI 0.89 to 1.22). Three trials combined showed statistically significant better quality of life with fesoterodine compared to ER tolterodine (SMD -0.20, 95%CI -0.27 to -0.14), higher reported cure or improvement (RR 1.11, 95%CI 1.06 to 1.16) and less symptoms. The analysis showed significantly higher withdrawals due to adverse events (RR 1.45, 95% CI 1.07 to 1.98) and dry mouth (RR 1.80, 95% CI 1.59 to 2.05) with fesoterodine compared to tolterodine..

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An analysis was also conducted comparing IR and ER dosage formulations. Extended versus immediate release preparations of oxybutynin or tolterodine, or both demonstrated no statistically significant differences for cure or improvement, leakage episodes or micturitions in 24 hours or withdrawals due to adverse events, but this was based on limited data. Overall, ER preparations had less risk of dry mouth at 2 to 12 weeks. When comparing ER preparations versus another ER preparation, there was less risk of dry mouth with ER tolterodine than oxybutynin (RR 0.75, 95% CI 0.59 to 0.95) but no difference between transdermal oxybutynin and ER oral tolterodine.

The authors concluded when the prescribing choice is between oral immediate release oxybutynin or tolterodine, there is evidence that tolterodine had less risk or dry mouth (RR 0.65, 95% CI 0.60-0.71) but no difference in efficacy outcomes. There is evidence of reduced risk of dry mouth with extended release preparations of oxybutynin or tolterodine compared to immediate release preparations. Between solifenacin and immediate release tolterodine, there were statistically significant differences for quality of life, patient reported cure or improvement, and urgency episodes in 24 hours, all favoring solifenacin. There was low evidence that solifenacin was associated with less risk of dry mouth compared to tolterodine. Between fesoterodine and extended release tolterodine, evidence from three trials demonstrated fesoterodine might be preferred for superior efficacy but has a higher risk of withdrawal due to adverse events and higher risk of dry mouth. There is little or no evidence available about long-term outcomes in these studies. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions. This review conducted both heterogeneity and sensitivity analyses. The authors evaluated for the risk of bias in included studies and found that: 1) allocation sequence was only adequately generated in 19 trials; 2) although 70 trials were double blinded, only 3 trials specifically stated the outcome assessors were blind to group allocation; 3) in 44 trials the evaluation of treatment efficacy was conducted based on intention-to-treat principals. Thirteen trials specifically stated that a per protocol analysis was used to assess treatment efficacy; 4) Thirty of the 86 trials (38%) declared pharmaceutical company support; 6) in the majority of included trials, the primary endpoint was measured after 12 weeks or less of treatment. Due to these limitations, the results of the review should be interpreted with caution. In addition to these potential biases, the short duration of most studies (12 weeks or less) and the lack of long-term follow up gave littler information about the long-term effects and tolerance of the different anticholinergic agents.

Agency for Healthcare Research and Quality (AHRQ)

A systematic review was performed to evaluate the treatment of overactive bladder in women.[6] This review found that the strength of the evidence for the management of OAB with pharmacologic treatment is weak to moderate for short term outcomes and weak for long term outcomes and harms. All treatments were effective at improving one or more OAB symptoms when compared to placebo. Reductions ranged from 0.9 to 4.6 in incontinence episodes per day across all drug treatments and from 0.7 to 4.2 in voids per day. Study by study, extended release formulations achieved modestly better effects than immediate release, statistical significance varied. No one drug was definitively superior to others[6] . As estimated by metaanalysis, extended release forms (taken once a day) reduce urinary urge incontinence by 1.78 (95 percent CI: 1.61, 1.94) episodes per day, and voids by 2.24 (95 percent CI: 2.03, 2.46) per day. Immediate release forms (taken twice or more a day) reduce UUI episodes by 1.46 (95 percent CI: 1.28, 1.64) per day, and voids by 2.17 (95 percent CI: 1.81, 2.54) per day. Of note, placebo reduces UUI episodes by 1.08 (95 percent CI: 0.86, 1.30), and voids by 1.48 (95 percent CI: 1.19, 1.71) per day. [6]

Fourteen RCTs were identified that directly compared pharmacologic agents. In the majority of comparisons, neither drug was reported more effective at reducing either incontinence episodes or voids per day with a few exceptions. Both oxybutynin ER and tolterodine ER demonstrated superiority in reducing urge incontinence episodes over tolterodine IR. Oxybutynin ER was more effective at reducing voids per day than tolterodine in IR or ER forms. [6] Given heterogeneity of participant populations and study designs, this limited number of studies is insufficient for any drug to be considered definitively superior.

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New Guidelines:

The American Urological Association was recently updated in 2012 for the diagnosis and treatment of overactive bladder in adults, based on a systematic review of the evidence through December 2011.[7] Quality assessment of individual trials was conducted by an evidence based practice center as well as the evidence strength for the body of evidence. A review of the evidence found no strong evidence for differential efficacy across medications. Therefore, the guidelines recommend the choice of medication be made based on patient's history of anti-muscarinic use, adverse event history, patient preferences, comorbidities, use of other medications, and available resources. Analysis did show different adverse event profiles for dry mouth and constipation. The rate of dry mouth for oxybutynin at 61.4% (95% CI: 52.5% to 69.5%) was statistically significantly higher than the 23.7% (95% CI: 20.7% to 26.9%) rate for tolterodine ($p<0.001$). The treatment recommendations are as follow:

First-Line Treatments:

- Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. *Standard (Evidence Strength Grade B)*
- Behavioral therapies may be combined with anti-muscarinic therapies. *Recommendation (Evidence Strength Grade C)*

Second-Line Treatments:

- Clinicians should offer oral anti-muscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium (listed in alphabetical order; no hierarchy is implied) as second-line therapy. *Standard (Evidence Strength Grade B)*
- If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. *Standard (Evidence Strength Grade B)*
- Transdermal (TDS) oxybutynin (patch or gel) may be offered. *Recommendation (Evidence Strength Grade C)*
- If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. *Clinical Principle*
- Clinicians should not use anti-muscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. *Clinical Principle*
- Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. *Clinical Principle*
- Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. *Expert Opinion*
- Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. *Clinical Principle*
- Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. *Expert Opinion*

New Safety Alerts, Indications:

Darifenacin (Enablex) ER has had recent FDA label changes in January and March of 2012. These changes include additions to the adverse reaction in term of anaphylactic reactions, erythema multiforme and interstitial granuloma annulare as well as additions to warnings and precautions about the associated with anticholinergic central nervous system effects.[8]

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In June of 2012, solifenacin succinate (Vesicare) was also noted to have central nervous system effects. The CNS anticholinergic effects that have been reported include headache, confusion, hallucinations and somonolence.[9]

In March 2012, the FDA changed the safety labeling of oxybutynin by adding glaucoma as an adverse reaction. Angioedema was added onto the warning section of oral oxybutynin's label in December of 2010.[10]

Fesoterodine (Toviaz) also received a warning for angioedema in February 2011. Later that year, in December, pruritis and urticaria were added under adverse reactions in the updated label of fesoterodine ER 4 mg tablets.[11]

New Drug Evaluation:

FDA approved indications:

Mirabegron (Myrbetriq™) was FDA approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Potential Off-label Use:

Mirabegron has evidence available for use in males with lower urinary tract symptoms and bladder outlet obstruction, on intraocular pressure in normotensive patients, and cardiac repolarization.[12]

Clinical Efficacy Data:

Approval and primary evidence for the efficacy of mirabegron was based on three randomized, double blind, phase III, placebo controlled, 12 week trials.[6]. The population of these studies included treatment naïve patients and patients who had been previously treated with OAB antimuscarinic therapy. All studies included a 2 week single-blind placebo run-in period followed by a 12-week double blind treatment period. The co-primary efficacy endpoints were change from baseline to final visit in mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. The secondary endpoints included change from baseline to final visit in mean volume voided per micturition, and change from baseline to week 4 in mean number of incontinence episodes and number of micturition per 24 hours[6]. Currently, only one of these studies has been published (Study 046) and is included in the evidence table below. The other two efficacy and safety trials have not been published, and therefore a critical appraisal was not performed. Study 046 also included an active control group (tolterodine SR 4 mg daily) to allow comparison to effect size, although this was not a comparative superiority trial.

Study 046 was a randomized, double-blind, placebo and active-control trial comparing the efficacy and safety of mirabegron 50mg (n=497), 100mg (n=498), and tolterodine 4mg SR (495) to placebo (n=497) after 12 weeks of treatment in 27 countries in Europe and Australia. No comparisons were made between mirabegron and tolterodine. The primary endpoints showed 1) A statistically significant difference in mean number of incontinence episodes per 24 hrs between placebo and treatment groups: mirabegron 50mg vs. placebo: -0.41 (p=0.003,CI -0.72,-0.09); mirabegron 100mg vs. placebo: -0.29 (p=0.010,CI -0.61,0.03); and tolteradine 4mg vs. placebo: -0.10 (p=0.11,CI -0.42,0.21); 2) Difference in mean number of micturition episodes per 24 hrs between placebo and treatment groups: mirabegron 50mg vs. placebo: -0.60 (p<0.001,CI -0.90,-.029); mirabegron 100mg vs. placebo: -0.44 (p=0.005,CI -0.74,-0.13); and tolteradine 4mg vs. placebo: -0.25 (p=0.11,CI -0.55,0.06).

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Clinical Safety:[6]
The safety of mirabegron was investigated in 1462 individuals in the phase 1 studies and 5863 patients in phase 2/3 studies, of which 622 patients with OAB received for at least 1 year. Serious adverse events, adverse events, and adverse events leading to permanent discontinuation of study drug were reported by 1.7%, 53.4% and 3.6% for mirabegron, 1.8%, 55.2%, and 2.9% for placebo, and 1.7%, 60.2% and 3.8% for tolterodine patients, respectively. There was no apparent dose response across mirabegron groups. Antimuscarinic side effects, specifically dry mouth, were reported less frequently in mirabegron-treated patients (2%) compared with tolterodine-treated patients (11.1%) in the 12 week trials and 2.6% versus 8.6% in the long-term study. Dry mouth was reported with a similar frequency in mirabegron-treated and placebo-treated patients in the 12 week studies. In these same studies, tachycardia and palpitations were reported as an AE in the mirabegron 50 mg group (1.2%; 0.4%) at a higher frequency than placebo (0.6%; 0.1%).

Mirabegron administered at 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute (bpm) compared with placebo in patients with OAB. In the phase 3 studies, a low proportion of mirabegron 50 mg-treated patients reported any occurrence of tachycardia (57/1375, 4.1%) at a frequency greater than placebo-treated patients (48/1380, 3.5%) and tolterodine-treated patients (16/495, 3.2%).

Mirabegron administered at the dose of 50 mg once daily was associated with a mean 0.4 to 0.6 mm Hg change from baseline systolic blood pressure/diastolic blood pressure (SBP/DBP) compared with placebo. Although there was no evidence of an increase in cardiovascular outcomes of death, serious adverse events, ventricular arrhythmias or major adverse cardiac events associated with mirabegron treatment compared to either placebo or tolterodine, due to the nature of short term studies, these result should be interpreted in caution.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Change in mean number of micturitions per 24 hrs
2) Change in mean number of incontinence episodes per 24 hrs
3) Quality of Life
4) Withdrawals due to adverse effects

Primary Study Endpoint:
1) Change from baseline in mean number of incontinence episodes
2) Micturitions per 24 hours

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Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Duration	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Study 046 Phase III, randomized double-blind, placebo-controlled trial	1. Mirabegron 50 mg daily 2. Mirabegron 100 mg daily 3. Tolterodine ER 4 mg daily 4. Placebo 12-week treatment duration	Demographics: Inclusion Criteria: OAB for at least 3 months, on average >8 micturitions per 24 hours, at least 3 episodes of urgency (grade 3/4) with or without incontinence in 3-day diary period, treatment naïve or prior anitmuscarinic therapy Exclusion Criteria:	ITT:1978 PP: Attrition:	2-week single-blind placebo run-in followed by 12-month double-blind treatment period	<u>Difference in mean number of incontinence episodes per 24 hrs:</u> M50 v P: -0.41 (p=0.003,CI -0.72,-0.09) M100 v P: -0.29 (p=0.010,CI -0.61,0.03) T4 v P: -0.10 (p=0.11,CI -0.42,0.21) <u>Difference in mean number of micturition episodes per 24 hrs:</u> M50 v P: -0.60 (p<0.001,CI -0.90,-.029) M100 v P: -0.44 (p=0.005,CI -0.74,-0.13) T4 v P: -0.25 (p=0.11,CI -0.55,0.06) Percentage of responders (patients with a 50% or greater decrease from baseline in the mean number of incontinence episodes per 24 h) M50: 72% M100: 67.6% Tolt: Pla: 60.1% M50 vs. Pla: OR 1.75, 95% CI 1.23-2.49; p=0.002 M100 vs. Pla: OR 1.45, 95% CI 1.02-2.05 P=0.037	N/A N/A	<u>Discontinuations due to adverse events:</u> M50: 25 (5%) M100: 16 (3.2% Tolt: 24 (4.8%) Pla: 13 (2.6%)	NS	**Quality Rating:** Good **Internal Validity: RoB** <u>Selection:</u> Randomization done using a computer-generated randomization scheme; allocation to groups was accomplished using an interactive response system. Similar baseline characteristics <u>Performance:</u> Patients were blinded t the identity of the study drug and investigators were blinded to identity of assigned drug. <u>Detection:</u> No information included i outcome assessors were blinded. <u>Attrition:</u> Total attrition approximately 10% and similar rates between groups. Efficacy was assessed using the full analysis set, which included all randomized patients who took at least one dose of the study drug and had at least a baseline and one post baseline micturition measurement, which included 96% of total randomized patients. **External Validity:** <u>Recruitment:</u> 27 countries in Europe and Australia <u>Patient Characteristics:</u> Approximately half of the patients had received previous treatment with OAB medication. <u>Outcomes:</u> Short-term only; not true effectiveness outcomes.

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Appendix 1: Specific Drug Information[13]

CLINICAL PHARMACOLOGY

Mirabegron is a beta-3 adrenergic receptor agonist. It relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 adrenergic receptor which increases bladder capacity. Stimulation of the beta-1 adrenergic receptor occurs at a mirabegron dose of 200mg.

PHARMACOKINETICS

The absorption and elimination pharmacokinetics of mirabegron are dose-dependent.

Parameter	Result
Oral Bioavailability	Dose dependent: 29% (25mg dose) and 35% (50mg dose)
Protein Binding	71% (albumin and alpha-1 acid glycoprotein)
Elimination	55% in urine and 34% in feces
Half-Life	50 hours
Metabolism	CYP3A4, CYP2D6, UGT, butylcholinesterase

DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
ER 25mg ER 50mg	Tab	PO	Daily	The daily dose should not exceed 25 mg in patients with severe renal impairment (CLcr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73m2); Not recommended in end stage renal disease	The daily dose should not exceed 25 mg in patients with moderate hepatic impairment (Child-Pugh Class B); Not recommended in severe hepatic impairment	The safety and effectiveness in pediatric patients have not been established	No dose adjustment is necessary for the elderly.	With or without food. Recommended starting dose is 25 mg once daily, which is effective within 8 weeks. The observed Cmax and AUC were approximately 40-50% higher in females compared to males. However, when normalized by body weight, it reduces to about 20-30%

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for mirabegron at this time.

Warnings and Precautions:

Mirabegron can increase blood pressure therefore periodic blood pressure readings are recommended, especially in hypertensive patients. It is not recommended for use in patients with severe uncontrolled hypertension, which is defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mmHg. Two recent studies found mirabegron associated with dose-related increases in supine blood pressure in healthy individuals. The maximum recommended dose of 50 mg was found to have a mean maximum increase in systolic/diastolic blood pressure of approximately 3.5/1.5 mmHg greater than placebo. In trials with OAB patients, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose was approximately 0.5 to 1 mmHg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in mirabegron patients.

Mirabegron may increase the chance of urinary retention in patients with bladder outlet obstruction (BOO) or patients taking antimuscarinic medications for the treatment of OAB. Clinical studies in patients with BOO did not demonstrate increased urinary retention in mirabegron patients, but mirabegron should still be administered with caution to patients with clinically significant Boo and in patients taking antimuscarinic medications for the treatment of OAB.

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates (e.g. metoprolol and desipramine) is increased when co-administered with mirabegron. Approriate monitoring and dose adjustment may be necessary, especially with drugs that are metabolized by CYP2D6 (e.g. thioridazine, flecainide, propafenone).

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
No look-alike/sound-alike drugs have been found to have error risk potential.

Adverse Reactions
Hypertension was the most common adverse reaction among the placebo and mirabegron study groups. The 50mg dose of mirabegron caused a similar amount of hypertension incidences to placebo whereas the 25mg mirabegron group had a higher incidence of hypertension in comparison to placebo.

	Placebo (%)	**Mirabegron 25mg (%)**	**Mirabegron 50mg (%)**
Number of Patients	**1380**	**432**	**1375**
Hypertension	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

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