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Drug Class Update with New Drug Evaluation: Overactive Bladder Drugs

Date of Review: August 2021

Date of Last Review: September 2018
Dates of Literature Search: 07/01/2018 - 04/21/2021
Brand Name (Manufacturer): Gemtesa® (Urovant Sciences, Inc.)
Dossier Received: yes

Generic Name: vibegron

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to identify and evaluate new evidence related to the treatment of overactive bladder (OAB) and determine the place in therapy for a newly approved OAB treatment.

Research Questions:
1. Is there any new high-quality comparative evidence on the efficacy and harms of therapies used for OAB?
2. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), for which a specific OAB therapy is more effective or associated with fewer harms?
3. What is the efficacy and safety of vibegron for the treatment of OAB?

Conclusions:
- There were 2 systematic reviews, 2 new guidelines, 1 new drug and 1 new formulation and 1 new indication identified since the last review. No new compelling evidence suggests clinically significant differences in efficacy between the pharmacotherapies for OAB. Anticholinergic treatments were consistently associated with a higher incidence of dry mouth.
- An Agency for Healthcare Research and Quality (AHRQ) evaluated nonsurgical treatment of urinary incontinence in women and found pharmacotherapy (e.g., antimuscarinics or beta-3 adrenergic agonists) to be effective for symptom management of OAB but when used alone were less effective than behavioral therapy.[1] There were no clinically relevant differences in efficacy between pharmacotherapies; however, anticholinergics were more commonly associated with dry mouth. In women 60 years and older with stress or urgency urinary incontinence (UUI), moderate quality evidence found anticholinergics to be more effective in improving symptoms than hormone therapy (OR 5.53; 95% CI, 1.03 to 29.56).[1]
- A good quality systematic review on the treatment of OAB in adults found small, but unlikely to be clinically impactful differences, between monotherapy treatments for OAB and monotherapy compared to combination treatments.[2] Changes in key outcomes (e.g., incontinence, urgency, and micturitions)

Author:

demonstrated absolute differences of less than half of an episode per day. Dry mouth was more often associated with antimuscarinics compared to mirabegron.[2]

- Guidance from the National Institute for Health and Care Excellence (NICE) and American Urology Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) supports current Oregon Health Authority (OHA) policy.
- A new beta-3 adrenergic agonist, vibegron, was approved for the use in adult patients with OAB. Improvements in daily micturitions were demonstrated in 2 phase 3 trials with daily reductions of -1.8 episodes with the vibegron 75 mg dose compared to -1.3 episodes for placebo (least square mean difference [LSMD] -0.5; 95% CI, -0.8 to -0.2; P<0.001).[3] Overall efficacy is modest and not clinically impactful for most patients.
- Common adverse events experienced with vibegron included headache, diarrhea, nausea and upper respiratory infection. Severe adverse events were rare and similar to placebo.[3]

Recommendations:

- Continue vibegron designation as non-preferred on the preferred drug list (PDL).
- No changes to the PDL are warranted based on the evidence identified since the last review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- This class was previously reviewed in September of 2018. No clinically significant efficacy or serious safety differences were found between therapies for OAB based on the findings of a Drug Effectiveness Review Project (DERP) report. Analysis of efficacy and costs resulted in no changes to the PDL.
- Oxybutynin and fesoterodine are preferred products on the PDL. Non-preferred products are subject to the general non-preferred drug prior authorization (PA) criteria. Almost 90% of the utilization in this class is for preferred products and the overall spend is not a significant contributor to OHA drug costs in the Fee-For-Service population.

Background:

OAB is a common condition with the highest prevalence in geriatric patients, affecting approximately 33% of those 75 years and older.[4] Guidelines define OAB as the presence of urinary urgency, often associated with frequency and nocturia, with or without UUI and without urinary tract infection or other pathology.[5,6] Urgency is the most common patient reported symptom of OAB and the most troubling symptom is incontinence, often reducing the quality of life in those affected. OAB related to incontinence is often referred to as "OAB wet" and patients without incontinence is referred to "OAB dry".[4] There are three types of urinary incontinence classifications: OAB with urgency incontinence (OAB wet); stress urinary incontinence; and mixed urinary incontinence with components of both OAB wet and stress urinary incontinence.[4] Stress incontinence is associated with involuntary urine loss on effort or physical exertion. Urinary symptoms can also arise from neurological conditions in the brain, spinal cord and peripheral nervous system.

Treatment of OAB includes non-pharmacological as well as pharmacological therapies. First-line recommendations are weight-loss, pelvic floor training, and biofeedback.[5] Behavioral therapy is very effective in patients with OAB and is often considered more effective by patients than pharmacological therapies. The combination of behavioral and pharmacological treatment has been shown to be more effective than placebo.[7] The use of pharmacologic treatments in OAB is limited by modest efficacy and poor tolerability due to adverse events. If drug treatment is warranted, guidelines recommend antimuscarinics (e.g., tolterodine, oxybutynin, solifenacin and darifenacin) or beta-3 adrenergic agonists (e.g., mirabegron) based on moderate evidence of efficacy.[5] There are no approved therapies for stress urinary incontinence; however, duloxetine is used off-label.[7]

Antimuscarinic therapies are recommended as first-line pharmacotherapy due to efficacy and cost.[7] A recent review by the AHRQ evaluated urinary incontinence in women and reported evidence that anticholinergics were more effective in cure, improvement and patient satisfaction compared to placebo based on high quality of evidence.[7] For the treatment of mixed urinary incontinence, duloxetine and tolterodine had evidence for efficacy in reductions in episodes based on low quality data. Other sources have found no difference in efficacy between antimuscarinic therapies for urinary incontinence.[8] Adverse events associated with antimuscarinics include: dry mouth, constipation, and dry/itchy eyes. Long-term use of antimuscarinics have been reported to possibly increase the risks of cognitive impairment and dementia.[4]

Beta-3 adrenergic agonists are a new class of therapies used for the treatment of OAB. Mirabegron was the first agent in the class approved by the Food and Drug Administration (FDA).[9] Evidence has demonstrated similar efficacy to antimuscarinics. Common adverse events associated with mirabegron use in clinical studies were hypertension, nasopharyngitis, urinary tract infection and headache. Mirabegron is not recommended for patients with severe uncontrolled hypertension (greater or equal to 180 mmHg/ 110 mmHg) due to dose related increases in supine blood pressure with a mean maximum increase of approximately 3.5 mmHg systolic and 1.5 mmHg diastolic greater than placebo.[10] Postmarketing data has demonstrated urinary retention in patients with bladder outlet obstruction (BOO) and in patients on antimuscarinic medications. Caution is advised if administering mirabegron to these patient populations.

Combination therapy with antimuscarinics and beta-3 adrenergic agonists can be used in patients refractory to monotherapy.[5] Studies evaluating mirabegron (25 mg and 50 mg) in combination with solifenacin 5 mg were found to be more effective than monotherapy by a difference in daily reductions in urinary incontinence episodes of -0.20 to -0.27, which are unlikely to be clinically significant.[11,12] Botulism toxin injections are an alternative therapy in patients with proven detrusor overactivity when less invasive therapies fail to control symptoms, but are associated with an increased risk of urinary tract infections and urinary dysfunction.[7] Surgical therapies can be offered as a third-line intervention.

Outcomes used to evaluate the efficacy of treatment in OAB are mostly subjective and associated with a high placebo response rate. Improvement or cure of UUI and number of daily micturitions are commonly used outcomes. A clinically meaningful response to patients is a reduction in UUI of 90% or more.[4] Clinical trials commonly use voiding diaries to measure urinary frequency by tracking micturitions (with around 7 micturitions a day considered normal), nocturia (waking due to the need to void) and UUI (involuntary leakage of urine associated with sudden need to void). The “need to urinate immediately” is an outcome used in the vibegron trials that has not been previously used for approval of other OAB agents. Quality of life, as measured by validated scales such as the Overactive Bladder Questionnaire (OAB-q) and Patient Global Impression Scale (PGI) are appropriate for assessing treatment effect on patient well-being. The OAB-q is separated into two sections: a validated 8-item symptom bother scale (SS) (score ranges from 0-100 in which higher scores indicate worse symptoms) and 25-item health-related quality of life (HRQL) scale rating subscales (e.g., coping, sleep, concern and social interaction)(score ranges 0-100 with high scores indicating improved quality of life).[13] The minimum important difference (MID) for the SS ranges from -13 to -25 and +5 to +12 for the HRQL.[14] The PGI is a reliable indicator of disease severity on activities of daily living and psychological well-being. Lower scores indicated improved quality of life.[15]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high

quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

AHRQ – Nonsurgical Treatments for Urinary Incontinence in Women

A systematic review and meta-analysis was done by AHRQ in 2018 to update findings from a 2012 report on the diagnosis and treatment of urinary incontinence in women.[1] Both stress and urgency incontinence were included. A systematic literature search of adult women with urinary incontinence was conducted from January 1, 2011 thru December 4, 2017 which identified 233 studies for inclusion. Evidence on non-pharmacological and pharmacological therapies was included. Pharmacological interventions included anticholinergics, onabotulinum toxin A, hormones (estrogen), alpha agonists, beta-3 agonists (no efficacy outcomes available for inclusion), antidepressants and periurethral bulking agents. The median age was 55 years old and median trial size was 85 participants.[1] Thirty-three trials were identified for stress incontinence, 16 for urgency incontinence and 4 with mixed stress/urgency incontinence. The primary outcome was the improvement and cure of urinary incontinence, as well as satisfaction with the treatment outcome and quality of life.

Stress incontinence is primarily treated with hormones or alpha agonists. Urgency incontinence treatments studied included tolterodine, oxybutynin, mirabegron, darifenacin, fesoterodine, flavoxate, phenylpropanolamine, pilocarpine, propantheline, and solifenacin. A network meta-analysis was used to combine results of study findings for urinary incontinence. Behavioral therapy was found to be effective in patients with stress incontinence compared to no therapy (OR 3.1; 95% CI, 2.2 to 4.4) and similar findings when used in combination with alpha agonists or hormones (OR 4.4; 95% CI, 1.4 to 13.8; moderate strength of evidence).[1]

There were 33 studies that informed findings for urgency incontinence. High quality evidence found behavioral therapy to be more effective for cure compared to no treatment or placebo (OR 2.75; 95% CI, 1.53 to 4.92).[1] Anticholinergics were also more effective than no treatment or placebo on cure rates based on high quality evidence (OR 1.80; 95% CI, 1.29 to 2.52). High quality of evidence demonstrated behavioral therapy to not be more effective to achieve cure compared to anticholinergics (OR 1.53; 95% CI, 0.90 to 2.60).[1] There were no direct comparisons of the combination of behavioral therapy and anticholinergics to no treatment or placebo.

In women who were 60 years and older with stress or UUI, moderate quality evidence found combination of behavioral therapy with hormones or neuromodulation was more likely to achieve cure compared to no treatment. Cure rates were higher in this population for behavioral therapy compared to anticholinergics (OR 2.76; 95% CI, 1.09 to 6.99) (moderate strength of evidence).[1]

Sixty-four studies provided evidence for the interventions to improve UUI. Behavioral therapy, anticholinergics and the combination of the two were more effective than no treatment based on high-quality evidence. Behavioral therapy was more likely to achieve improvement in UUI compared to anticholinergics (OR 4.2; 95% CI, 1.6 to 10.9) (high strength of evidence).[1]

In older women (60 years and older) with stress or UUI, anticholinergics were more likely to have symptom improvement than those patients who used hormone therapy (OR 5.53; 95% CI, 1.03 to 29.56) based on moderate quality evidence.[1]

In women with UUI, patient satisfaction was higher with behavioral therapy compared to anticholinergics (OR 8.2; 95% CI, 1.7 to 39.4) based on high quality of evidence. There is moderate quality of evidence that compared to no treatment, anticholinergics alone were more effective in achieving satisfaction (OR 2.6; 95% CI, 2.1 to 3.3).[1] In older women, behavioral therapy and anticholinergics were more effective in controlling UI symptoms compared to no treatment based on moderate evidence.

There was high quality evidence that dry mouth was the most common adverse event associated with the use of anticholinergics.[1]

Hsu, et al – Updating the Evidence on Drugs to Treat Overactive Bladder

A high quality systematic review and meta-analysis looked at the evidence for the treatment of OAB.[2] The original review was conducted in consultation with the Drug Effectiveness Review Project (DERP) with an updated search following the same process. The evidence was searched from 2012 to September 2018 which identified 51 studies. Evidence was included for adult patients with OAB with UUI and mixed incontinence. Exclusion criteria included patients with stress incontinence or neurogenic detrusor overactivity. Drugs included in the search were the following: darifenacin, fesoterodine, mirabegron, oxybutynin, solifenacin, tolterodine, and trospium. Twenty of the studies were new since the original DERP report. Five were good quality, 10 were fair quality and 5 were poor quality due to unclear allocation concealment, blinding and missing data. A majority of participants were female (77%), 59.2% had previous pharmacotherapy for OAB and the average duration of OAB symptoms was 67.4 months.[2] The outcomes of interest were: incontinence episodes in 24 hours, 3-days with no incontinence, urgency episodes in 24 hours, and micturitions in 24 hours.

Results for the findings of the meta-analysis are reported in **Table 1**. Only statistically significant findings are listed. There were no significant differences for any outcomes between mirabegron 50 mg and tolterodine ER 4 mg based on 3 studies. Solifenacin was compared to oxybutynin which demonstrated no difference for the outcomes of urgency episodes in 24 hours and micturitions in 24 hours. Combination therapy with mirabegron and solifenacin was more effective for all outcomes compared to solifenacin alone; however, the differences were small and unlikely to be clinically impactful. Both groups were found to have clinically meaningful changes in OAB-q Symptom Bother score. The combination was also more effective than mirabegron alone except for the outcome of no incontinence over 3 days. Comparisons between mirabegron and solifenacin found solifenacin to be more effective at reducing incontinence and micturitions. Mirabegron and solifenacin were both found to achieve minimal clinically important differences (MCID) for the OAB-q Symptom Bother score and solifenacin had significantly better scores than mirabegron. Dry mouth was consistently more common with solifenacin compared to mirabegron throughout all the studies. Overall, the evidence suggests minimal clinical difference in efficacy between monotherapy comparisons and combination treatment compared to monotherapy for the treatment of symptoms of OAB.

Table 1. Results for Efficacy Outcomes for the use of Treatments in OAB[2]

Comparison	Outcome	Result*
Mirabegron 50 mg + Solifenacin 5 mg Vs. Solifenacin 5 mg	Incontinence episodes in 24 hours	-0.18 (95% CI, -0.31 to -0.05)
	3-day 0 incontinence	RR 1.23 (95% CI, 1.13 to 1.34)
	Urgency episodes in 24 hours	-0.58 (95% CI, -0.89 to -0.28)
	Micturitions in 24 hours	-0.41 (95% CI, -0.54 to -0.27)
Mirabegron 50 mg + Solifenacin 5 mg	Incontinence episodes in 24 hours	-0.34 (95% CI, -0.52 to -0.16)

Vs. Mirabegron 50 mg	Urgency episodes in 24 hours	-0.77 (95% CI, -1.02 to -0.52)
	Micturitions in 24 hours	-0.56 (95% CI, -0.75 to -0.37)
Mirabegron 50 mg Vs. Solifenacin 5 mg	Incontinence episodes in 24 hours	+0.20 (95% CI, 0.02 to 0.38)
	Micturition in 24 hours	+0.18 (95% CI, 0.01 to 0.35)
Fesoterodine 8 mg Vs. Tolterodine 4 mg	Incontinence episodes per 24 hours	-0.18 (-0.29 to -0.07)
	3-day 0 incontinence	RR 1.10 (95% CI, 1.04 to 1.16)
	Urgency episodes in 24 hours	-0.40 (95% CI, -0.69 to -0.12)
	Micturitions per 24 hours	-0.22 (95% CI, -0.43 to -0.01)
Solifenacin 5 mg Vs. Tolterodine 4 mg	Incontinence episodes in 24 hours	-0.36 (95% CI, -0.58 to -0.13)
	Urgency episodes in 24 hours	-0.49 (95% CI, -0.79 to -0.20)
Tolterodine Vs. Oxybutynin	3-day 0 incontinence	RR 0.73 (95% CI, 0.55 to 0.97)
Key: * All results statistically significant		
Abbreviations: RR = relative risk		

After review, 9 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–24]

New Guidelines:
High Quality Guidelines:

NICE – Urinary Incontinence and Pelvic Organ Prolapse in Women

A 2019 guideline on the management of women with urinary incontinence and pelvic organ prolapse was produced by NICE.[25] First-line recommendations were for the use of bladder training for at least 6 weeks for women who have urgency or mixed urinary incontinence. Combination therapy of OAB medication with bladder training should be considered if frequency is a bothersome symptom and there is not satisfactory benefit from bladder training programs alone. If medication is being considered, the patient should be counseled on expected efficacy, common adverse events, and the need for up to 4 weeks of therapy to see substantial benefit and anticholinergic use long-term may affect cognitive function. The anticholinergic with the lowest acquisition cost should be recommended to women with OAB or mixed urinary incontinence in women. An alternative medication can be offered to women who do not experience relief with the first medication, after at least 4 weeks of therapy. Offer transdermal OAB treatment to women who are unable to tolerate oral medications. Mirabegron is recommended for patients with OAB in which antimuscarinic drugs are contraindicated, clinically ineffective or have unacceptable adverse reactions.[26] It is not recommended to use flavoxate, propantheline, or imipramine for OAB or urinary incontinence. Oxybutynin (immediate release) should not be recommended to older women who may be at risk of sudden deterioration in their physical or mental health. The use of desmopressin may be considered for patients with OAB and urinary incontinence who have nocturia; however, use with caution in patients with cystic fibrosis and in those 65 years or older with cardiovascular (CV) disease or hypertension. In women with stress urinary incontinence, the use of duloxetine is not recommended first-line and should be used

second-line in women who prefer pharmacological therapy to surgical treatment. The use of systemic hormone treatment is not recommended; however, intravaginal estrogens can be offered to treat OAB in postmenopausal women with vaginal atrophy. Women 75 years and older should have OAB medications reviewed every 6 months and all other women should be evaluated annually.

AUA/SUFU – Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) In Adults

In 2019 AUA/SUFU updated their guidance on the treatment of OAB in adults.[5] The systematic review and data extraction was done as part of the AHRQ Evidence Report/Technology Assessment. Conflicts of interest with industry were present for all authors. The publication was extensively peer reviewed. The guideline focus was for diagnosis and management of OAB with literature current through October 2018. An amendment followed the initial guidance to include recommendations on the use of combination therapy in patients with OAB.[6] Individual quality studies were graded according to Evidence-based practice center and the body of evidence was assigned a strength rating of A (high), B (moderate) or C (low). Insufficient evidence on additional treatment information was designated as a Clinical Principle or Expert Opinion.[5]

Pharmacotherapy recommendations for patients with OAB are outlined in **Table 2**. Dose modification or use of a different antimuscarinic or beta-3 adrenergic agonist is recommended for patients who have inadequate symptom control or adverse reactions to initial therapy. Antimuscarinics should not be used in patients with narrow-angle glaucoma unless approved by an ophthalmologist. Patients who have impaired gastric emptying or history of urinary retention should be very cautious about using antimuscarinics. Antimuscarinics should be used cautiously in patients if already taking therapies with anticholinergic properties. Both antimuscarinics and beta-3 adrenergic agonists should be used with caution in patients that are frail with OAB.

Table 2. AUA/SUFU Treatment Recommendations for Overactive Bladder[5,6]

Recommendation	Grade
First-Line	
Behavioral therapies (e.g., bladder training, control strategies, pelvic floor muscle training, fluid management	B
Behavioral therapies may be combined with pharmacological therapies	C
Second-line	
Oral antimuscarinics or beta-3 adrenergic agonist are recommended	B
ER formulations should be used, if available, over IR due to a lower incidence of dry mouth	B
Transdermal oxybutynin (patch or gel) can be offered	C
Combination therapy with an antimuscarinic and beta-3 adrenergic agonist can be considered for patients refractory to monotherapy with either antimuscarinics or beta-3 adrenergic agonist	B
Abbreviations: ER – extended release; IR – immediate release	

After review, 2 guidelines were excluded due to poor quality.[27,28]

New Formulations or Indications:

Mirabegron (Myrbetriq) –Received FDA-approval for 2 new indications since the last review.

1) In March of 2021 mirabegron received FDA approval for use in pediatric patients 3 years and older, weighing 35 kg or more, with neurogenic detrusor overactivity (NDO).[10] Mirabegron tablets and mirabegron granules (used in oral suspension) are not interchangeable and should not be combined. For pediatric patients weighing less than 35 kg, mirabegron granules should be used (recommendations from prescribing material despite approval for patients 35 kg or more). For pediatric patients weighting more than 35 kg the recommended starting dose is for mirabegron 25 mg orally once daily. After 4 to 8 weeks the dose can be increased to 50 mg daily. The recommended starting dose of mirabegron granules is 6 ml (48 mg) of the extended-release oral suspension orally once daily. After 4 to 8 weeks the dose can be increased to 10 ml (80 mg) once daily.

Mirabegron granules were studied in a 52-week, open-label trial in 86 pediatric patients (ages 3-17 years) with NDO and involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H_2O and patients or caregivers practiced clean intermittent catheterization (CIC).[10] The primary endpoint was change from baseline in patients' maximum cystometric (bladder) capacity (MCC) measured at 24 weeks. Patients were stratified by age: 3 years to less than 12 years (n=43) and 12 years to 17 years (n=25). The MCC was increased 72 ml (95% CI, 45 to 99) in patients 3-12 years and 113 ml (95% CI, 79 to 147) in patients 12-17 years.[10]

2) In 2018 mirabegron was approved for use in combination with solifenacin succinate for adult patients with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.[10] Two, 12-week double-blind, randomized controlled trials provided evidence for approval. Combination therapy was found to reduce incontinence episodes by -0.25 (95% CI, -0.49 to -0.01) to -0.20 (95% CI, -0.44 to 0.04) compared to solifenacin monotherapy. Differences from mirabegron monotherapy ranged from -0.34 (95% CI, -0.58 to -0.10) to -0.23 (95% CI, -0.47 to 0.01).[10] Overall differences were small and unlikely to be clinically impactful.

Solifenacin (Vesicare LS) – solifenacin is an oral suspension approved in May of 2020 for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 2 years and older.[29] Solifenacin LS dosing is weight based with the oral suspension available as a 1 mg/mL solution. Approval was based off of 2 small, 52-week, open-label studies which included a total of 95 patients. The primary endpoint was change in patients' maximum cystometric (bladder) capacity (MCC) after 24 weeks. An increase of 39-57 mLs was demonstrated with solifenacin LS in patients 2 to 17 years.[29]

New FDA Safety Alerts:

No safety alerts identified.

Randomized Controlled Trials:
A total of 41 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Vibegron (Gemtesa®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Vibegron (Gemtesa®) is FDA approved for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency.[30] Vibegron is the second beta-3 adrenergic receptor agonist approved for use in OAB.[30] Vibegron selectively stimulates the beta-3 adrenergic receptor in the bladder to increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

Summary of Clinical Efficacy:
Vibegron is the second beta-3 adrenergic receptor agonist approved for use in OAB.[30] Vibegron selectively stimulates the beta-3 adrenergic receptor in the bladder to increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling. Vibegron was studied in 2 phase 3, double-blind, placebo-controlled, randomized trials in adult patients with OAB, EMPOWUR and a second study by Yoshida, et al. (**Table 5**).[3,31] Patients in EMPOWUR had to meet the inclusion criteria of an OAB diagnosis by a physician while the second study enrolled patients with a history of OAB symptoms. The second study did not allow patients with uncontrolled hypertension, while EMPOWUR had no such exclusionary criteria. The mean patient age ranged from 59-63 years and a majority of participants were female (85-90%). Seventy percent of patients had a wet OAB diagnosis, defined as 1.0 or more UUI episodes per day, in both studies. EMPOWUR was comprised of predominately white participants (78%) while the second study enrolled Japanese patients. Only 14% percent of patients enrolled in EMPOWUR and 18% of patients in the second study had previously used pharmacotherapy for OAB, suggesting mild disease.[2,31] The primary endpoint in both trials was the mean number of daily micturitions. An additional co-primary endpoint in EMPOWUR was the average daily number of UUIs (in patients with wet OAB), which was a secondary endpoint in the second study.[3,,3] Additional secondary endpoints were daily urgency episodes, urgency incontinence episodes, and quality of life.

Both trials used a 2-week single-blind placebo run-in period and a 12-week double-blind treatment period. The EMPOWUR study (n=1,518) randomized patients to vibegron 75 mg, placebo or tolterodine ER in a 5:5:4 ratio by a central, web based interactive response system.[2] The second study randomized 1,224 patients in a 3.3:3.3:3.3:1 ratio to vibegron 50 mg, vibegron 100 mg, placebo or imidafenacin (only available in Japan).[3] In the EMPOWUR study patients recorded symptoms (e.g., micturitions, urgency, incontinence, and cause of incontinence) in a paper voiding diary (PVD) at baseline and at the end of treatment weeks 2, 4, 8 and 12. The second study recorded a 3-day micturition diary before each scheduled visit and the King's Health Questionnaire (KHQ) was administered at week 0 and week 12.[31] Patient satisfaction was measured via the Patient Global Impression (PGI) instrument.

Overall results suggest only mild to moderate efficacy of vibegron for the treatment of OAB. The average daily number of micturitions was reduced by -1.8 episodes in patients taking vibegron 75 mg compared to -1.3 episodes for patients taking placebo (LSMD -0.5; 95% CI, -0.8 to -0.2; P<0.001) in EMPOWUR and by -2.08 for vibegron 50 mg, -2.03 for vibegron 100mg, and -1.21 for placebo in the second study (p<0.001 for both doses of vibegron compared to placebo) (**Table 5**).[3] Results from a 52-week, double-blind extension study comparing vibegron to tolterodine support findings from the 12-week studies.[32] Reduction in micturitions demonstrated daily reductions for vibegron and tolterodine, -2.4 and 2.0, respectively (p-value not reported).[32] The MCID for reductions in average daily micturitions is -3.0 to -3.5 based on the Patient Global Impression (PGI) Severity Scale and -2.7 to -3.0 on the PGI-Frequency scale based on FDA analysis of study data.[4] Reduction in micturitions of -0.5 to -0.86 a day demonstrated with vibegron compared to placebo would suggest that the change would not be clinically meaningful for most patients.

The second co-primary endpoint in EMPOWUR, average daily number of UUI episodes, was decreased with vibegron by -2.0 compared to -1.4 for placebo (p<0.001), with smaller reductions in the second study with a change of -1.35 in the vibegron 50 mg group, -1.47 in the vibegron 100 mg group and -1.08 for placebo (p=0.001 and p<0.001, respectively).[2,3] In patients with wet OAB, the proportion of wet OAB cases with 75% or greater reduction in average number of

UUI episodes was higher with vibegron 75 mg compared to placebo, 52.4% versus 36.8%, respectively (P<0.001; ARR 15.6%/NNT 7).[2] Efficacy for the reduction in UUI episodes was sustained out to 52 weeks with decreases of -2.2 episodes in patients treated with vibegron 75 mg and -1.7 for tolterodine (p<0.05).[4]

For the bothersome symptom of frequency of daily urgency episodes, vibegron 75 mg decreased episodes by -2.7 a day from a baseline value of around 7.75 episodes a day.[2] This was in comparison to a decrease of -2.0 for placebo, which resulted in a statistically significant change, favoring vibegron, of LSMD -0.7 (95% CI, -1.1 to -0.2; P=0.0020), which is unlikely to be clinically impactful.[2] Results from the second study reiterate frequency findings with a reduction of -2.28 for vibegron 50 mg, -2.44 for vibegron 100 mg and -1.77 for placebo (P<0.001 for both comparisons).[3]

Quality of life outcomes were improved with vibegron compared to placebo. The OAB-q coping score, bother score and total score along with the PGI-severity score were secondary outcomes in EMPOWUR. Vibegron increased coping scores by 16.5 points compared to 12.9 points for placebo, (LSMD 3.6; 95% CI, 1.2 to 6.0; p=0.0039).[33] The HRQL total score was improved 14.6 points with vibegron and 10.8 with placebo (LSMD 3.8; 95% CI, 1.7 to 5.8; p<0.001). An improvement of around 3% is unlikely to be clinically impactful. Symptom bother scores were reduced -19.6 points with vibegron compared to -12.8 points with placebo (LSMD -6.9; 95% CI, -9.2 to -4.6; p<0.0001).[33] Both PGI-severity and PGI-control scores were reduced more with vibegron compared to placebo, -0.2 and -0.3 points, respectively (p<0.0001).[33] The second study found patients taking pharmacotherapy were "very much satisfied" based on the PGI more often than patients taking placebo; 59.5% for vibegron 50 mg, 62.0% for vibegron 100 mg and 37.1% for placebo.[31]

There is insufficient evidence to determine if vibegron is more effective than current treatment for OAB. In the EMPOWUR study tolterodine was used as an active control and imidafenacin was used as an active control in the second study. Daily reductions in mean micturition episodes were similar between vibegron 75 mg and tolterodine (-1.8 and -1.6, respectively) and vibegron 100 mg and imidafenacin (-2.03 and -2.06, respectively). These studies were not designed to detect statistical differences between the groups. Results would suggest minimal clinical differences, with no substantial benefit of vibegron over other therapy used for OAB.

Limitations to the findings include a placebo run-in which could select out patients that are more adherent to therapy. Patients who had no prior use of anticholinergics experienced the largest reduction in UUIs and accounted for the majority of patients enrolled in the study. In clinical practice anticholinergics are considered first-line pharmacotherapy and therefore the benefit seen outside the study setting would be expected to less than what was demonstrated in the trials. Manufacturer funding and authors with conflicts of interest may introduce additional bias. External validity is reduced due to high enrollment of white patients (78%) in the EMPOWUR study and inclusion of only Japanese patients in the second study. Additional details on trial methodology would have benefited the quality of both trials, EMPOWUR being a fair quality trial and the second study considered to be poor quality. FDA clinical evaluation of vibegron concluded that only some patients would have a clinically meaningful response to vibegron and vibegron is not considered more efficacious than currently available therapies.

Clinical Safety:

Summary of Clinical Safety:

Safety data from product labeling report the most common treatment-emergent adverse event (TEAEs) with vibegron occurring at a rate of 2% or more and higher than placebo, to be headache, diarrhea, nausea and upper respiratory infection (**Table 3**).[30] Treatment discontinuation due to adverse events were reported in 1.7% of patients treated with vibegron compared to 1.1% treated with placebo and 3.3% treated with tolterodine ER.[3] The most common reason for discontinuation was headache in the vibegron group and dry mouth in the tolterodine group. The incidence of severe adverse events was low in trials with one cerebrovascular accident in both vibegron 75 mg and tolterodine and one patient with pneumonia in both the vibegron 75 mg group and with placebo.[5] Severe

adverse events occurring in only the vibegron 75 mg group include the following: abdominal pain (n=1), appendix disorder (n=1), atrial fibrillation (n=1), cardiac failure congestive (n=1), colitis (n=1), colorectal adenocarcinoma (n=1), noncardiac chest pain (n=1) and pleural effusion (n=1).[5] Blood pressure changes (mean maximum increase of approximately 3.5 mmHg systolic and 1.5 mmHg diastolic greater than placebo) experienced with mirabegron have not been demonstrated with vibegron (no clinically significant changes in blood pressure in clinical trials).[10,30]

Table 3. Adverse Reactions in Patients Treated with Vibegron Occurring in ≥ 2% of Patients and Exceeding Placebo Rate[30]

Adverse Reaction	Vibegron 75 mg (n=545)	Placebo (n=540)
Headache	4%	2.4%
Nasopharyngitis	2.8%	1.7%
Diarrhea	2.2%	1.1%
Nausea	2.2%	1.1%
Upper respiratory tract infection	2.0%	0.7%

An extension study evaluating safety endpoints at 52 weeks of treatment found a low incidence of serious adverse events with vibegron therapy (0.4%) compared to tolterodine ER (0.9%).[32] Discontinuations due to study medications were 1.5% for vibegron and 3.4% for tolterodine ER. The most common adverse reactions were hypertension, 8.8% for vibegron and 8.6% for tolterodine ER, and urinary tract infection, 6.6% for vibegron and 7.3% for tolterodine ER.[32] Vibegron demonstrated an increased incidence in diarrhea compared to tolterodine ER, 4.8% versus 1.7% and upper respiratory infection, 3.7% versus 0.4%. Tolterodine ER had an increased risk of dry mouth (5.2%) compared to vibegron (1.8%).[32]

Vibegron increases the systemic exposure of digoxin and therefore digoxin concentrations should be monitored before and during concomitant therapy. No other notable drug interactions are associated with vibegron use. The use of vibegron is not recommended in patients with a eGFR <15 mL/min/1.73 m^2 (with or without dialysis) or in patients with severe hepatic impairment (Child-Pugh C).[30]

Safety data is limited by the small number of participants exposed to vibegron in clinical trials (n=3190), exclusion of patients with uncontrolled hypertension, and lack of data on patient comorbidities. Unanswered safety questions include the use in pediatric populations and in women who are pregnant or breast feeding. Post-marketing data has indicated safety concerns of urinary retention, rash/allergic skin reactions and constipation. Incidence and severity of these adverse events are unknown. Vibegron use beyond 52 weeks has not been studied.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reductions in daily micturitions
2) Reduction in urgency episodes
3) Urinary incontinence cure (wet OAB patients)
4) Urinary incontinence improvement (wet OAB patients)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Average daily number of micturitions
2) Average daily number of urge urinary incontinence episodes

Table 4. Pharmacology and Pharmacokinetic Properties[30]

Parameter	
Mechanism of Action	Selective human beta-3 adrenergic receptor agonist. Activation of the beta-3 adrenergic receptor increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.
Oral Bioavailability	Not reported Food has no effect on absorption
Distribution and Protein Binding	Volume of distribution: 6304 L Protein binding: 50%
Elimination	59% fecal and 20% urine
Half-Life	30.8 hours
Metabolism	CYP3A4 is the most common enzyme responsible for in vitro metabolism. Metabolism plays a minor in the overall elimination of vibegron.

Table 5. Clinical Efficacy Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Staskin, et al[3,4] EMPOWUR Phase III, MC, DB, PC	1. Vibegron 75 mg daily 2. Placebo daily 3. Tolterodine ER 4 mg daily 2-week single-blind placebo run-in 12-week double-blind treatment period	Demographics: Age: 62 yrs. old Female: 85% White: 78% U.S. sites: 90% Patients with wet OAB*: 77% Median micturitions/day: 10.51 Median urgency episodes/day: 7.92 Key Inclusion Criteria: - 18 years or older - History of OAB for at least 3 months and diagnosed by a physician - At least 75% meeting wet OAB criteria and up to 25% meeting dry OAB criteria Key Exclusion Criteria:	ITT 1. 526 2. 520 3. 417 Attrition 1. 54 (10%) 2. 45 (8%) 3. 46 (11%)	**Co-Primary Endpoints:** Co-primary endpoint change from baseline to week 12: Average daily number of micturitions: 1. -1.8 episodes 2. -1.3 episodes 3. -1.6 episodes Vibegron vs. Placebo: LSMD -0.5 (95% CI, -0.8 to -0.2; P<0.001) Tolterodine ER vs. Placebo: LSMD -0.3 (95% CI, -0.6 to 0.1; P=0.0988) Average daily number of UUI episodes (wet OAB patients): 1. -2.0 episodes 2. -1.4 episodes 3. -1.8 episodes Vibegron vs. Placebo: LSMD -0.6 (95% CI, -0.9 to -0.3; P<0.001)	NA NS NA	Hypertension: 1. 9 (1.7%) 2. 9 (1.7%) 3. 11 (2.6%) Discontinuations due to adverse events: 1. 9 (1.7%) 2. 6 (1.1%) 3. 14 (3.3%) Serious adverse events: 1. 8 (1.5%) 2. 6 (1.1%) 3. 10 (2.3%) p-value not reported for safety outcomes	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: Low. Randomized in a 5:5:4 ratio by central, web based interactive response system. Stratified by sex and by wet vs. dry OAB. Baseline characteristics were well matched apart from patients in the vibegron group were slightly older and there were fewer male patients in the placebo group compared to the other groups. Double-dummy design was used to mask treatment allocation. Performance bias: Unclear. Blinding of providers and investigators was stated but not clearly described. Detection bias: Unclear. Outcome assessment was not reported. Patient reported symptoms in diary and interpretation of results may be subject to bias. Attrition bias: Low. Attrition between groups was low and similar between groups. Data was analyzed based on FAS with multiple imputation for missing data.

	4- week safety evaluation	- Urine output of greater than 3000 mls in 24 hours in past 6 months or in run-in phase - Lower urinary tract pathology that could be associated with urgency, frequency, or incontinence - History of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatment for BPH within 6 months of screening - post-void residual volume of >150 mL - 3 or more UTIs per year		Tolterodine ER vs. Placebo: LSMD -0.4 (95% CI, -0.7 to -0.1; P=0.0123) **Secondary Endpoint(s):** Frequency of daily urgency episodes: 1. -2.7 episodes 2. -2.0 episodes 3. -2.5 episodes Vibegron vs. Placebo: LSMD -0.7 (95% CI, -1.1 to -0.2; P=0.0020) Tolterodine ER vs. Placebo: LSMD -0.4 (95% CI, -0.9 to -0.0; P=0.0648) Proportion of wet OAB cases with 75% or greater reduction in average number of UUI episodes†: 1. 52.4% 2. 36.8% 3. 47.6% Vibegron vs. Placebo: (confidence interval not reported; P<0.001) Tolterodine ER vs. Placebo: (confidence interval not reported; P<0.05)	NA NA NS ARR 15.6/ NNT 7 ARR 10.8/ NNT 10			Reporting bias: High. Outcomes reported as prespecified; however, many outcomes that were evaluated (presented in FDA review) were not reported in published study. Other Bias: High. Manufacturer funded. All authors had conflicts of interest. **Applicability**: Patient: Results are most applicable to white females who are 65 years of age and older with wet OAB and treated in the US. Extensive exclusion criteria limiting applicability to many patient with OAB. Intervention: Vibegron dose of 75 mg was appropriate based on dosing studies. Comparator: Placebo comparator is appropriate; however, formal comparative analysis with tolterodine ER would help define vibegron place in therapy for the treatment of OAB. Outcomes: Outcomes used were appropriate for efficacy analysis of OAB treatments. Urinary incontinence cure rates for patients with wet OAB is an important outcome that was not reported. Quality of life is an important endpoint in patients with OAB and was evaluated but not reported in published study. Setting: This was a multi-center trial in 6 countries. Ninety percent of participants were from the U.S.
2. Yoshida, et al[31] Phase III, MC, DB, PC, PG	1. Vibegron 50 mg daily 2. Vibegron 100 mg daily 3. Placebo 4. Imidafenacin 0.1 mg twice daily	Demographics: Age: 59 yrs. old Female: 90% Japanese: 100% Patients with wet OAB*: 78% Previous OAB therapy: 18% Key Inclusion Criteria: - 20 years or older - History of OAB symptoms for 6 or more months	ITT 1. 370 2. 368 3. 369 4. 117 Attrition 1. 16 (4%) 2. 12 (3%) 3. 13 (4%) 4. 4 (3%)	**Primary Endpoint:** Change in mean number of micturitions/day from baseline at week 12: 1. -2.08 2. -2.03 3. -1.21 4. -2.06 Vibegron 50 mg vs. placebo: -0.86 (95% CI, -1.12 to -0.60; P<0.001) Vibegron 100 mg vs. placebo: -0.81 (95% CI, -1.07 to -0.55; P<0.001)	NA NA	Hypertension: 1. 0 (0%) 2. 0 (0%) 3. 0 (0%) 4. 2 (1.7%) Discontinuations due to adverse events: 1. 3 (0.8%) 2. 2 (0.5%) 3. 1 (0.3%) 4. 1 (0.9%)	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: Unclear. Randomized in a 3.3: 3.3: 3.3:1 ratio. Details not provided on strategy for randomization. Stratified by sex, prior OAB treatment, wet vs. dry OAB and mean micturitions at baseline. Treatment blinding was maintained by using a double-dummy design. Performance bias: Unclear. No details on blinding of providers and investigators were provided. Detection bias: Unclear. No details on binding of outcome assessors. Patient reported symptoms in diary and

	2-week placebo single-blind run-in 12-week double-blind treatment period	- 8 or more micturitions a day and either 1 or more urgency episodes per day or 1 or more urgency incontinence episodes per day - Ability to use restroom without support - Normal ECG Key Exclusion Criteria: - Ruled out by study investigator - Cancer within 5 years - Systolic BP of 160 mmHg or greater, diastolic BP 100 or greater or pulse of 110 bpm or greater - Severe cardiac, liver, kidney or blood disorder - Unable to take anticholinergic or beta-adrenergic therapy - History of possible cause of urinary disorder - Post-void residual urine volume (PVR) of 100 ml or more		**Secondary Endpoints:** Change from baseline in daily urgency episodes: 1. -2.28 2. -2.44 3. -1.77 4. -2.15 Vibegron 50 mg vs. placebo: -0.51 (95% CI, -0.76 to -0.25; P<0.001) Vibegron 100 mg vs. placebo: -0.67 (95% CI, -0.93 to -0.42: P<0.001) Change from baseline in daily urgency incontinence episodes: 1. -1.35 2. -1.47 3. -1.08 4. -1.51 Vibegron 50 mg vs. placebo: -0.27 (95% CI, -0.44 to -0.10; P=0.001) Vibegron 100 mg vs. placebo: -0.39 (95% CI, -0.55 to -0.22; P<0.001) Change from baseline in daily incontinence episodes: 1. -1.40 2. -1.53 3. -1.10 4. -1.47 Vibegron 50 mg vs. placebo: -0.30 (95% CI, -0.49 to -0.12; P=0.001) Vibegron 100 mg vs. placebo: -0.43 (95% CI, -0.61 to -0.24; P<0.001) Change from baseline in nocturia episodes: 1. -0.58 2. -0.62 3. -0.47 4. -0.63	NA NA NA NA NA NA	Serious adverse events: 1. 1 (0.3%) 2. 1 (0.3%) 3. 3 (0.8%) 4. 1 (0.9%) p-value not reported for safety outcomes		interpretation of results may be subject to bias. Attrition bias: Low. Attrition was low and similar between groups. Data was analyzed based on the FAS. No details on how missing data was handled. Reporting bias: Low. Outcomes reported as prespecified. Other Bias: High. Manufacturer funded. All authors had conflicts of interest. **Applicability**: Patient: The results of the study are most applicable to women with wet OAB that have not received previous drug therapy and are Japanese. Intervention: Vibegron 50 mg and 100 mg are appropriate dosing regimens. Comparator: Placebo comparator is appropriate; however, formal comparative analysis with imidafenacin would help define place in therapy for vibegron treatment of OAB. Outcomes: Outcomes used were appropriate for efficacy analysis of OAB treatments. Setting: One hundred and nine sites in Japan.

				Vibegron 50 mg vs. placebo: -0.11 (95% CI, -0.21 to -0.02; P=0.016) Vibegron 100 mg vs. placebo: -0.16 (95% CI, -0.25 to -0.06; P=0.001) <u>Patients "very much satisfied" on PGI at week 12:</u> 1. 220 (59.5%) 2. 228 (62.0%) 3. 137 (37.1%) 4. 67 (57.3%) Vibegron 50 mg vs. placebo: 22.4% (95% CI, 15.3% to 29.4%; P<0.001) Vibegron 100 mg vs. placebo: 24.9% (95% CI, 17.8% to 31.8%; P<0.001)	NA NA NA NA			

<u>Abbreviations</u>: AC = active controlled; ARI = absolute risk increase; ARR = absolute risk reduction; BPH = benign prostatic hypertrophy; CI = confidence interval; DB = double-blind; ER = extended release; ITT = intention to treat; FAS = full analysis set; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; OAB = over active bladder; PC = placebo controlled; PG = parallel group; PP = per protocol; RR = relative risk; UTI = urinary tract infection; UUI = urge urinary incontinence.
Key: * Wet OAB was defined as an average of 8.0 or more micturitions and 1.0 or more UUI episodes per day as determined during the run-in phase; † Results provided for patients with wet OAB

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Appendix 1: Current Preferred Drug List

Generic	Brand	For	Route	PDL
fesoterodine fumarate	TOVIAZ	TAB ER 24H	ORAL	Y
oxybutynin	OXYTROL	PATCH TDSW	TRANSDERMAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE	SYRUP	ORAL	Y
oxybutynin chloride	DITROPAN XL	TAB ER 24	ORAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE ER	TAB ER 24	ORAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE	TABLET	ORAL	Y
darifenacin hydrobromide	DARIFENACIN ER	TAB ER 24H	ORAL	N
darifenacin hydrobromide	ENABLEX	TAB ER 24H	ORAL	N
flavoxate HCl	FLAVOXATE HCL	TABLET	ORAL	N
mirabegron	MYRBETRIQ	TAB ER 24H	ORAL	N
oxybutynin	OXYTROL FOR WOMEN	PATCH TD 4	TRANSDERMAL	N
oxybutynin chloride	GELNIQUE	GEL PACKET	TRANSDERMAL	N
solifenacin succinate	VESICARE LS	ORAL SUSP	ORAL	N
solifenacin succinate	SOLIFENACIN SUCCINATE	TABLET	ORAL	N
solifenacin succinate	VESICARE	TABLET	ORAL	N
tolterodine tartrate	DETROL LA	CAP ER 24H	ORAL	N
tolterodine tartrate	TOLTERODINE TARTRATE ER	CAP ER 24H	ORAL	N
tolterodine tartrate	DETROL	TABLET	ORAL	N
tolterodine tartrate	TOLTERODINE TARTRATE	TABLET	ORAL	N
trospium chloride	TROSPIUM CHLORIDE ER	CAP ER 24H	ORAL	N
trospium chloride	TROSPIUM CHLORIDE	TABLET	ORAL	N
vibegron	GEMTESA	TABLET	ORAL	N

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to April 21, 2021
Search Strategy:

#	Searches	Results
1	oxybutynin.mp.	1597
2	fesoterodine.mp.	281
3	darifenacin.mp.	358
4	flavoxate.mp. or Flavoxate/	190
5	mirabegron.mp.	639
6	solifenacin.mp. or Solifenacin Succinate/	779
7	tolterodine.mp. or Tolterodine Tartrate/	1097
8	trospium.mp.	328
9	vibegron.mp.	37
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	3826
11	limit 10 to (english language and humans and yr="2018 -Current")	331
12	limit 11 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	41

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GEMTESA® safely and effectively. See full prescribing information for GEMTESA.

GEMTESA (vibegron) tablets, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
GEMTESA is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dose is one 75 mg tablet once daily. (2.1)
- Swallow tablet whole with water. (2.1)
- Tablet may be crushed and mixed with applesauce. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 75 mg (3)

----------CONTRAINDICATIONS----------
Do not use if prior hypersensitivity reaction to vibegron or any components of the product. (4)

----------WARNINGS AND PRECAUTIONS----------
Urinary Retention: Monitor for urinary retention, especially in patients with bladder outlet obstruction and also in patients taking muscarinic antagonist medications for OAB, in whom the risk of urinary retention may be greater. If urinary retention develops, discontinue GEMTESA. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%) reported with GEMTESA were headache, urinary tract infection, nasopharyngitis, diarrhea, nausea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Urovant Sciences, Inc., at 1-833-876-8268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Digoxin: Measure serum digoxin concentrations before initiating GEMTESA. Monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect. (7)

----------USE IN SPECIFIC POPULATIONS----------
Pediatric use: Safety and effectiveness in pediatric patients have not been established. (8.4)
End-stage Renal Disease with or without Hemodialysis: Not recommended. (8.6)
Severe Hepatic Impairment: Not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with overactive bladder
Intervention	Antimuscarinic and beta-3 adrenergic agonists
Comparator	Active treatment or placebo
Outcomes	Daily micturitions, urgency episodes, urinary incontinence, safety and quality of life
Setting	Outpatient