Long-Term Care Updates

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New Drug Review: Vibegron (GEMTESA)

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Introduction

Vibegron was FDA-approved in December 2020. It is indicated for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency, and urinary frequency.[1]

Pharmacology:

Vibegron is a selective beta-3 adrenergic receptor agonist. In activating this receptor, the detrusor smooth muscle is relaxed during bladder filling, thereby increasing bladder capacity.[1]

Pharmacokinetics:

Maximum serum concentrations of vibegron are achieved within 1-3 hours after administration, and exposure to vibegron, including C_{max} and AUC, increases in a greater than dose-proportional manner. Steady state concentrations are reached within 7 days. Vibegron has minimal metabolism via CYP3A4 and is 50% plasma protein bound. Its half-life is around 31 hours. The pharmacokinetics of vibegron are not impacted by administration with a high-fat meal or by crushing the tablet and administering with applesauce. Age, sex, race/ethnicity, renal function, and hepatic function do not appear to alter vibegron's pharmacokinetic parameters; however, vibegron has not been studied in patients with severe renal or hepatic impairment.[1]

Standard of Care/Clinical Guidelines:

The American Urological Association (AUA) published comprehensive guidelines for the diagnosis and treatment of OAB (non-neurogenic) in adults in 2013.[2] Amendments to the guidelines to account for new research were published in 2015 and 2019.[3,4] Taken together, the guidelines and subsequent amendments recommend a patient-centered approach to selection of appropriate pharmacotherapy, weighing potential benefits and risks. Initially, OAB should be managed with behavioral interventions, if possible. These may be combined with pharmacologic management when needed.[2-4] Per the 2015 guideline amendment, appropriate pharmacotherapy can include an oral antimuscarinic or oral beta-3 adrenergic receptor agonist.[3] Because antimuscarinics have been associated with significant adverse effects including cognitive deficits, the AUA recommends that antimuscarinics be used with extreme caution in patients with dementia and that they may be contraindicated entirely depending on the level of cognitive impairment.[2] At the time of publication of the guideline amendments, mirabegron was the only beta-3 adrenergic receptor agonist

on the market, and the AUA noted that mirabegron appeared to offer similar efficacy to the antimuscarinics with a lower risk for dry mouth and constipation.[3] The 2019 guideline amendment addressed the use of combination therapy, noting that combination therapy with an antimuscarinic and a beta-3 adrenergic receptor agonist is appropriate for patients refractory to monotherapy.[4] The AUA also suggests that dose modifications or switching between drugs within the same class should be considered in patients who experience inadequate symptom control or unacceptable adverse events with any one therapy. For carefully-selected and thoroughly-counseled patients with moderate-to-severe symptoms who do not respond to behavioral interventions plus oral pharmacotherapy, intradetrusor onabotulinumtoxinA, peripheral tibial nerve stimulation, or sacral neuromodulation can be considered.[3]

The Society for Post-Acute and Long-Term Care Medicine (AMDA) clinical practice guidelines for the management of Urinary Incontinence in the Long-Term Care Setting were last revised in 2012.[5] These explicitly state that immediate release oxybutynin therapy is not appropriate in the long-term care setting. The following agents are listed as potential pharmacologic interventions for the treatment of urge incontinence: darifenacin, fesoterodine, solifenacin, tolterodine, and trospium. Patients should receive an adequate trial period of pharmacologic therapy before switching to another agent; it can take up to 3 months for patients to experience the full benefit of some treatments. AMDA guidelines briefly mention mirabegron, approved around the time of publication, as a potential alternative to anticholinergic treatments for OAB and note that, at the time of guideline preparation, there were no known geriatric-specific concerns which would limit the use of mirabegron in the elderly population.[5]

Given the date of publication, vibegron's place in therapy is not described in the guidelines above; however, it would be reasonable to place it alongside mirabegron as an alternative beta-3 adrenergic receptor agonist.

Comparative Clinical Efficacy:

Vibegron was FDA-approved on the basis of one 12-week, phase III clinical trial (EMPOWUR) that included 1518 adult patients with OAB (see Table 2). In this study, vibegron 75mg once daily was compared to tolterodine extended release 4mg and placebo. After 12 weeks, daily micturitions decreased by 0.5, daily urgency episodes decreased by 0.7, and volume voided/micturition increased by 21.3mL with vibegron vs. placebo ($p \leq 0.002$ for all). Additionally, in patients with wet OAB, daily UUI episodes decreased by 0.6 vs. placebo ($p < 0.001$), and these patients had a 42% greater relative risk of achieving a ≥75% reduction in daily UUI episodes with vibegron vs. placebo. For every 7 patients with wet OAB receiving vibegron over placebo, one additional patient reached this endpoint.[6] Vibegron was also found to improve quality of life scores when compared with placebo.[7] While a statistical comparison between vibegron and tolterodine was not conducted, vibegron showed numerical improvements over tolterodine for all of the efficacy-related endpoints above.[6] A subpopulation analysis of the EMPOWUR study found similar results in patients ≥65 years of age, suggesting that vibegron works as well or better in elderly patients.[8] Earlier studies also confirmed the safety and efficacy of vibegron in patients with OAB.[9,10] However, these trials evaluated different patient populations (e.g., Japanese subjects) and/or unapproved doses of vibegron (e.g., 3mg, 15mg, 50mg, 100mg).

The long-term safety and efficacy of vibegron was established from an extension of the EMPOWUR trial that included 505 patients receiving either vibegron or tolterodine for 52 weeks. On average, vibegron reduced daily micturitions by 2.4, urgency episodes by 3.4, and incontinence episodes by 2.5 when compared to baseline. Vibegron was superior to tolterodine with respect to the improvement in daily incontinence episodes (-2.5 vs. -1.9; $p < 0.05$). Additionally, vibegron decreased the mean number of daily UUI episodes vs. tolterodine in patients with wet OAB (-2.2 vs. -1.7; $p < 0.05$). Approximately 50% of patients in each group saw a ≥50% reduction in urgency episodes, and, in patients with wet OAB, 61.0% receiving vibegron vs. 54.4% receiving tolterodine reported a ≥75% reduction in daily UUI episodes.[11]

Adverse Reactions:

Vibegron was generally well-tolerated in the EMPOWUR study. Eight patients (1.5%) receiving vibegron reported serious adverse events, and 9 patients (1.7%) discontinued treatment with vibegron due to an adverse event. Adverse event-related discontinuation was similar to placebo (1.1%) and lower than tolterodine (3.3%). While not common, urinary retention was reported in 0.6%, 0.7%, and 0.4% of patients receiving vibegron, tolterodine, and placebo. The most common adverse reactions reported include headache (4.0%), nasopharyngitis (2.8%), diarrhea (2.2%), and nausea (2.2%).[6]

With the exception of dry mouth, rates of adverse reactions in elderly patients in the EMPOWUR study were similar to those reported in the complete study population. Additionally, cardiovascular adverse events were rare, with rates similar to placebo.[8]

An extension of the EMPOWUR study provides evidence related to rates of adverse reactions when vibegron is taken long-term. While the extension study did not include a placebo group, results indicate that vibegron continues to be well-tolerated when compared with tolterodine when taken for at least one year. In the extension period (40 weeks), 1.5% of patients taking vibegron and 3.4% taking tolterodine discontinued treatment due to adverse effects. Additionally, 3.3% of patients taking vibegron and 4.3% taking tolterodine experienced one or more treatment-emergent serious adverse effects.[11]

QT Prolongation:

Vibegron does not prolong the QTc interval. A single 390mg dose of vibegron (5.2 times the usual dose) did not affect cardiac electrophysiology.[1]

Contraindications, Warnings & Precautions:

Labeled contraindications, warnings, and precautions for vibegron include hypersensitivity (contraindication) and urinary retention (warning/precaution). Patients receiving vibegron should be monitored for signs and symptoms of urinary retention, as this adverse effect has been reported with its use. The risk for urinary retention may be greater in patients taking vibegron with anticholinergic drugs for OAB. Vibegron should be discontinued in patients who develop urinary retention.[1]

Drug Interactions:

While vibegron is a CYP3A4 substrate, this isoenzyme plays a minor role in its metabolism, and *in vitro* drug interaction studies show no clinically relevant interactions between strong CYP3A4 inducers or inhibitors and vibegron. Additionally, while vibegron is a P-glycoprotein (P-gp) substrate, it does not appear to interact with P-gp inhibitors. Administration of vibegron with digoxin has been shown to increase the Cmax and AUC of digoxin by 21% and 11%, respectively. While vibegron does not have anticholinergic properties, urinary retention has been rarely reported in patients taking vibegron.[1] Theoretically, concomitant use of vibegron with anticholinergic drugs might increase the risk for urinary retention.[12]

Recommended Monitoring:

All patients should be monitored for improvement in symptoms of OAB, including urinary incontinence, urgency, and frequency. No laboratory monitoring is required for vibegron.[12]

Geriatric/Nursing Considerations:

Of the 526 patients who received vibegron in the phase 3 EMPOWUR trial, 46% were ≥65 years of age and 14% were ≥75 years of age. No differences in safety or efficacy outcomes were reported between patients ≥65 years of age and younger patients.[1,8]

Vibegron tablets may be crushed, mixed with a tablespoon of applesauce, and taken immediately with a glass of water in patients with difficulty swallowing oral tablets.[1]

Dosing and Availability:[1]

Vibegron is available as a 75mg tablet.

Usual Adult Dosage: 75mg once daily with or without food.

Renal Dosing:

Mild or moderate renal impairment (eGFR 15 to <90mL/min/1.73m^2): No adjustment needed

Severe renal impairment (eGFR <15mL/min/1.73m^2 (with or without hemodialysis)): Use not recommended

Hepatic Dosing:

Mild or moderate hepatic impairment (Child-Pugh Class A and B): No adjustment needed

Severe hepatic impairment (Child-Pugh Class C): Use not recommended

Geriatric Dosing: Refer to renal and hepatic dosing as appropriate.

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