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Gemtesa® (Vibegron): Freeing Patients from Overactive Bladder

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Overactive bladder (OAB), also known as urinary incontinence (UI), is defined by the International Continence Society as "symptom syndrome suggestive of lower urinary tract dysfunction".[1] Overactive bladder is more specifically defined as urinary urgency typically accompanied by frequency and nocturia with or without urge urinary incontinence (UUI) in the absence of urinary tract infection (UTI) or other obvious neurologic conditions.[2,3] This condition is not classified as a disease but a group of urinary symptoms that can affect patient's quality of life (QoL), quality of sleep, and mental health.[4,5] An estimated 42.2 million American adults are affected by OAB, which tends to be the most common in the elderly with 30-50% suffering from this condition.[6,7] The prevalence of UUI and OAB symptoms are also higher in females.[5,8]

There are four main symptoms of OAB: urgency, frequency, nocturia, and UI.[3] Urgency is defined as "complaint of a sudden, compelling desire to pass urine which is difficult to defer".[2] Urinary frequency can be measured via bladder diary and normal voiding is considered to be up to seven micturition episodes per day.[3] However, this range is variable depending on fluid intake, hours of sleep, and other comorbid conditions or other factors.3 Nocturia is defined as interruption of sleep one or more times per night due to the need to void.[2,3] Lastly, UI is defined as involuntary leakage of urine that is associated with a sudden desire of void.[3]

Diagnosis of OAB is based on the four main symptoms, however differentiation from other conditions such as UTI, polydipsia, diabetes insipidus, cognitive problems, and bladder pain syndrome, should be conducted.[3] A urinalysis, Mini-Mental State Examination (MMSE) and physical examination are potential tools for differentiation. Additionally, diagnoses should also consider the patient's current medication list as several drugs can impact patient's urinary activity. Diagnosis is often done by clinical principles or expert opinion due to insufficient literature.

Behavioral therapy is first-line treatment.[3] Examples of behavioral therapies are bladder diaries which document voiding behavior, caffeine reduction, fluid intake modification, weight reduction bladder training, and pelvic floor muscle training.1 Among those options, bladder diaries quantify baseline symptom levels and treatment effects that may be used to determine treatment efficacy or balance between symptom control and adverse events.[3] Second-line treatment options include medication therapy which target three different receptors: M3, alpha-1, and beta-3.[9] Oral or transdermal anti-muscarinic agents such as tolterodine, oxybutynin, fesoterodine, darifenacin, solifenacin, and trospium for antimuscarinic agent and mirabegron (a beta-3-adrenergic receptor agonist) may be used when treating OAB.[3] Third-line treatments, intradetrusor onabotulinumtoxin A, are considered to be invasive due to increased risk of infection, increased post-void residual, and potential need for self-catheterization that may not be reversible.[3]

Gemtesa® (vibegron), is a new beta-3-adrenergic receptor agonist that was approved by the FDA in December 2020 for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency in adults.[10] Current guidelines have not yet included vibegron in treatment algorithms. Mirabegron, the only other medication in this class, is however recommended as the second line treatment along with OAB treating antimuscarinic agents.[3]

Pharmacology

Mechanism of Action

Vibegron is a selective beta-3 receptor agonist, which results in relaxation of detrusor smooth muscle during bladder filling to increase bladder capacity.10 Beta-3-adrenergic receptors are found in the lower urinary tract at the level of the detrusor muscle and the urothelium. The stimulation of this receptor in the detrusor muscle results in smooth muscle relaxation causing attenuation of bladder contractility reducing urge incontinence.[9]

Pharmacokinetics

The median time to maximum concentration (Tmax) of vibegron is achieved within approximately one to three hours with food consumption not significantly changing rate and extent of absorption regardless of fasting or non-fasting state.[10] A dose-proportional increase was seen in the maximum concentration

IN THIS ISSUE

(Cmax) and area under the concentration-time curve (AUC) up to 600mg with eight-times of the approved recommended dose. The mean volume of distribution (Vd) was 6,304 liters and human plasma protein binding was approximately 50%. Vibegron is a CYP3A4 and p-glycoprotein (P-gp) substrate, however these had a minor role in metabolism and elimination. Vibegron is excreted 20% renally (19% as unchanged) and 59% (54% as unchanged) via feces. The half-life of vibegron is 30.8 hours.10 Select pharmacokinetic properties are summarized in **Table 1**.

Table 1 | Select Vibegron Pharmacokinetics[10]

Absorption	
T_{max}[a]	1-3 hours
C_{max}[b]	~100%
T_{ss}[c]	~7 days
Distribution	
Vd[d]	97.4 L
Protein Binding	≥ 99%
Metabolism	
CYP3A4, P-gp[e] substrate	
Elimination	
$T_{1/2}$[f]	30.8 hours
Fecal	59%
Urine	20%

[a]Time to maximum concentration; [b]Maximum concentration; [c]Time to steady state; [d]Volume of distribution; [e]P-glycoprotein; [f]Half-life

Clinical Trials

The FDA approval of vibegron was based off of a single phase III randomized controlled trial.[13] This section will summarize this clinical trial along with a Phase IIb trial which evaluated the efficacy, safety, and tolerability and phase III trial conducted in Japan which also evaluated safety and efficacy.[14,15] **Table 2** shows the results of the primary endpoints for these trials with **Table 3** depicting the secondary results of EMPOWUR trial.

EMPOWUR

Staskin D, et al conducted a phase III clinical trial, EMPOWUR, that was a 12-week, randomized, placebo- and active-comparator, double-blinded, multi-center international clinical trial in the US, Poland, Hungary, Canada, Latvia, and Lithuania.[13] The purpose of the trial was to evaluate the efficacy, safety, and tolerability of vibegron. The inclusion criteria consisted of patients 18 years or older with a history of OAB, diagnosed for three or more months before screening. These patients documented occurrences in a voiding diary which described either wet or dry OAB, such as urinary urgency with or without UUI. Wet OAB was defined as eight or more micturition and one or more UUI episodes per day and dry OAB as eight or more micturition, three or more urgency episodes, and less than one UUI episodes per day. Patients were excluded if volume of urine output was greater than 3,000 mL. Selected patients underwent one to five weeks of a screening period with a 28-day washout, two weeks of patient side single blinded placebo run in, 12 weeks double blinded randomized treatment period, and a four week follow up for safety evaluation. These patients were trained to document urinary symptoms/issues in diaries. These were collected during the double-blind treatment run-in-period then during week two, four, eight , and twelve. This voiding diary consisted of micturition, urgency, incontinence and whether incontinence episodes were by urge or other reasons.

There were two co-primary endpoints, which were change from baseline to week 12 in average daily number of micturition and average daily number of UUI episodes in those with wet OAB. The key secondary endpoints were change from baseline to week 12 in the average daily number of urgency episodes, average volume voided per micturition, and proportion of wet OAB cases with 75% or higher reduction in the average daily number of UUI episodes.

A total 3,149 patients were enrolled, then after screening and the run-in period, 1,518 patients were randomized at a 5:5:4 ratio to vibegron 75 mg orally one tablet once every morning , placebo, or tolterodine ER 4 mg one tablet orally once daily, respectively. Randomization was stratified by sex and by wet vs. dry OAB. Among randomized patients, 90.4% (n=1373) of patients completed the trial and 96.4% (n=1463) of patients contributed data. Baseline characteristic were well distributed by age, sex, race, region, OAB categories, and median micturition/day, urgency episodes/day, and mL volume voided/micturition.

The micturition frequency from baseline to 12 weeks was reduced by -0.5 episodes per day in the vibegron group compared to the placebo group (-1.8 vs -1.3; 95% CI -0.8 to -0.2; p<0.001). A difference of -0.3 episodes per day was seen when comparing the tolterodine group to the placebo group (-1.6 vs -1.3; 95% CI -0.6 to -0.1; p=0.0988) which was not significantly different. The other co-primary endpoint, change from baseline at 12 weeks of UUI episodes frequency, was reduced by -0.6 episodes in the vibegron group compared to the placebo group (-2.0 vs -1.4; 95% CI -0.9 to -0.3; p<0.0001). The tolterodine group also found a statistically significant reduction of -0.4 episodes compared to the placebo group (-1.8 vs -0.6; 95% CI -0.8 to -0.2; p<0.0123). There was no direct comparison in between the intervention group and the active comparator group.

Frequency of urgency episodes was significantly reduced by -0.7 episodes per day in the vibegron group compared to the placebo group (-2.7 vs -2.0; 95% CI -1.1 to -0.2; p<0.002). The tolterodine was not found to be significantly different compared to the placebo group (-2.5 vs -2.0; 95% CI -0.9 to -0.0; p<0.0648). Change in volume voided per micturition was significantly improved by 21.2mL in the vibegron group compared to the placebo group (23.5 mL vs 2.2 mL; 95% CI 14.3 to 28.1; p<0.0001). This was also improved in the tolterodine arm (13.3mL) compared to the placebo group (15.5 mL vs 2.2 mL ; 95% CI 5.9 to 20.7; p<0.001). More participants with in wet OAB in the vibegron group reported a 75% or higher reduction from baseline in UUI episodes per day in the vibegron group compared to the placebo group (15.6%; 52.4% vs 36.8%; p<0.0001). This was also seen to a lesser extent in the in the tolterodine group compared to the placebo group (10.8; 47.6% vs 36.8%; p<0.05).

Adverse events in the vibegron group, such as the events with incidence greater than 2.0% and higher than placebo, were headache (4.0% vs. 2.4%), nasopharyngitis (2.8% vs. 1.7%), diarrhea (2.2% vs 1.1%), and nausea (2.2% vs. 1.1%). For tolterodine group, dry mouth (6.5% vs. 0.9%), hypertension (2.6% vs 1.7%), headache (2.6% vs 2.4%), nasopharyngitis (2.6% vs. 1.7%) and diarrhea (2.1% vs 1.1%) were observed as greater incidence than 2.0% and higher than placebo.

Vibegron group was superior to placebo group in all primary

and secondary endpoints with statistically significant value. In contrast, tolterodine group did not achieve statistically significant result compared to placebo group in the change from baseline at 12 weeks of micturition frequency and frequency of urgency episodes. There was no direct comparison in between vibegron group and tolterodine group, therefore superiority or inferiority among these groups could not be identified. Of note, the editor mentioned that the efficacy of these two options is comparable.[13]

Phase IIb trial

Micheson et al conducted a randomized, double-blinded placebo and active comparator controlled, parallel group, two-part superiority trial that was done at 169 sites in 18 countries.[14] This study was separately conducted in two parts with a first part being eight weeks of a dose finding study and a second part being four weeks of a study to obtain an additional data such as assessing the efficacy, safety, and tolerability. Each part had one to three weeks of screening, one-week of placebo run-in, treatment period, then two weeks of follow up. The inclusion criteria were diagnosed for OAB for three months or more before screening. After the run-in period, the first part of patients (n=987) was randomized adequately into placebo (n=141), vibegron 3mg (n=144), vibegron 15mg (n=134), vibegron 50mg (n=150), vibegron 100mg (n=149), tolterodine ER 4mg (n=135), and vibegron 50mg plus tolterodine ER 4mg (n=134) (V3, V15, V50, V100, TER4, V50 + TER/V50 respectively). The second part of patients (n=408) was also adequately distributed by 1:2:2:2 ratio to one of the following four treatment groups: placebo (n=64), vibegron 100mg (n=112), tolterodine ER 4mg (n=122) , and vibegron plus tolterodine ER 4 mg (n=134). The voiding diary was completed for seven and more days before each visit and efficacy assessed at week one, two, four, and eight entries. Wet OAB and dry OAB were defined as same as EMPOWUR trial.[13]

The primary endpoint was the change from baseline to week eight in daily number of micturition in all patients of the first part of study. One of the secondary endpoints was change from the baseline to week four in number of micturition in all patients of the second part of study. Other secondary endpoints were the change from baseline to week four (second part) and eight (first part) in a LSM daily UUI episodes, number of total incontinences, and number of urgency episodes.

A total of 1,395 patients were randomized, 1,393 received study medications, and 1,324 (94.9%) completed the trial. The mean population age in the entire trial was 58.6 years old, 89.7% of the patients were women, 80.6% were OAB wet, 20.6% were Japanese living in Japan, and 63.6% never received anticholinergic therapy for OAB.

The treatment group of V50 and V100 from the first part of study resulted in statistically significant improvement in the primary endpoint. The number of micturition from baseline to week eight was reduced by -0.64 and -0.91 episodes per day in the V50 and V100 compared to placebo (-1.87 vs -1.09, -2.11 vs -1.09; p=0.007, p<0.001, respectively). In the secondary endpoints, the daily number micturition from the baseline to week four had a statistically significant difference of -0.79 episodes per day in V100 (from second part of study) compared to placebo (-1.95 vs -1.20; p=0.009). For the other secondary endpoints, UUI episodes, and number of total incontinences, and number of urgency episodes, V50 and V100 were all statistically significant improved from baseline to week eight (difference in LSM: -0.72, -0.71; p<0.05. -0.60, -0.58; p<0.05. -0.76, -1.24; p<0.05 respectively). In the second part of study, the V50/TER4 group statistically significant decreased from baseline to week four the LSM daily number of micturition, UUI, total incontinence, and urgency episodes compared to TER4 alone (-0.91, -0.53, -0.51, -1.27; p<0.001, p=0.027, p=0.038, p<0.001 respectively). The V50 and V100 group achieved a statistically significant decrease in average number of daily micturition (CI 95%, -0.53 [-0.93, -0.12] and -0.52 [-0.93, -0.12], respectively) and urgency episodes (-0.61 [-1.18, -0.04] and -0.72 [-1.30, -0.15]) compared with placebo as early as week 2. All the other intervention group or active comparator group that are not listed has not shown statistically significant differences.[14]

Phase III – Japan

The trial conducted by Yoshida M, et al was a multicenter, randomized, four-arm, parallel-group, placebo- and active- con-

Table 2 | Primary Outcomes from Vibegron Trials[13-15]

Trial	Outcomes	Intervention	Result (95% CI[a])	P-Value
EMPOWUR	Change from baseline to week 12 in the average daily number of micturition	Placebo	-1.3	-
		Vibegron 75mg	-1.8	-0.5 (p<0.001)
		Tolterodine ER 4mg	-1.6	-0.3 (p=0.098)
	Change from baseline to week 12 in the average daily number of UUI episodes with wet OAB	Placebo	-1.4	-
		Vibegron 75mg	-2.0	-0.6 (p<0.0001)
		Tolterodine ER 4mg	-1.8	-0.4 (p<0.0123)
Phase IIb[a]	Dose-related reductions in the LSM daily number of micturition in all patients at week eight in part 1	Placebo	-1.09	-
		Vibegron 50mg	-1.78	-0.64 (p=0.007)
		Vibegron 100mg	-1.81	-0.91 (p<0.001)
		Tolterodine ER 4mg	-1.73	-0.54 (p=0.026)
Phase III—Japan	Change in the mean micturition per day at week 12 from baseline	Placebo	-1.21	-
		Vibegron 50mg	-2.08	-0.86 (p<0.001)
		Vibegron 100mg	-2.03	-0.81 (p<0.001)

[a]Only statistically significant values are included.

trolled phase III trial in patients with OAB done completed in Japan.[15] The two-week placebo run in phase was single-blinded and the treatment phase was double-blinded. Key inclusion criteria were OAB symptoms for six or more months, age of 20 or over, and no clinically significant abnormal ECG. Eligible patients entered two-week placebo run-in phase and received two tablets of vibegron placebo and one tablet of imidafenacin placebo in the morning and evening. After the run-in phase, patients were randomly assigned in a 3.3:3.3:3.3:1 ratio to one of the following four treatment groups: vibegron 50mg once daily, 100mg once daily, placebo, or imidafenacin 0.1mg twice daily. These groups were adjusted for sex, prior treatment for OAB (use/no use of anticholinergic or beta-3-adrenergic agonist), OAB wet and dry, and baseline mean micturitions. Wet OAB was defined as one or more mean UUI at baseline and OAB dry was defined as less than one mean UUI at baseline.

The primary endpoint was a change in the mean micturition per day at week 12 from baseline. The secondary endpoints were changes from baselines to each visit in daily mean micturition, urgency episodes, UUI episodes, incontinence episodes, nocturia episodes, and voided volume per micturition. Patient satisfaction levels were assessed at the end of treatment by using a self-administered Patient Global Impression (PGI). Those levels were satisfied to very much improved, much improved, and minimally improved, and very much satisfied which included very much improved and much improved.

A total of 1,474 patients were enrolled, 1,232 patients were randomized, and 1,230 received one or more doses of study drug. Majority of study population were female which was about 90%, and mean age was around 58 years old among four comparison arms. Baseline patient characteristics were adequately distributed to each group. In all groups, 99.7% or more patients were with adherence of 75% or higher during the double-blind treatment phase.

Vibegron 50mg and 100mg treatment groups resulted in significant improvements in both primary and secondary efficacy outcomes compared with placebo. Micturition per day at week 12 from baseline was reduced by -2.08 episodes/day in the vibegron 50mg group -0.86 episodes/day (-1.12, -0.60; p<0.001), -2.03 episodes/day the vibegron 100mg group -0.81 episodes/day (-1.07, -0.55) vibegron 100mg ($p < 0.001$) vs -1.21 episodes/day in the placebo group. For the secondary endpoints, number of daily urgency episodes, UUI episodes, incontinence episodes, nocturia episodes, and voided volume per micturition, vibegron 50mg and 100mg were all significantly improved ($p < 0.001$) compared with

Table 2 | Secondary Outcomes from Vibegron Trials[13,15]

Trial	Interventions	Outcomes	Mean Change from Baseline	LSM treatment difference vs. placebo (95% CI[a])	P-Value
EMPOWUR	Placebo	Average daily number of urgency episodes per day	-2.0	-	-
			-2.7	-0.7 [-1.1, 0.2]	p<0.002
			-2.5	-0.4 [-0.9, 0.0]	p<0.0648
	Vibegron 75mg	Average volume voided per micturition	2.2 mL	-	-
			23.5 mL	21.2 mL [14.3, 28.1]	p<0.0001
			15.5 mL	13.3 mL [5.9, 20.7]	p<0.001
	Tolterodine ER 4mg	Proportion of wet OAB cases with 75% or greater reduction in the average daily number of UUI episodes	36.8%	-	-
			52.4%	15.6%	p<0.0001
				47.6%	10.8
Phase III—Japan	Placebo	Urgency episodes/day	-1.77	-	-
			-2.28	-0.51	P<0.001
			-2.44	-0.67	P<0.001
		Urgency incontinence episodes/day	-1.08	-	-
			-1.35	-0.27	P=0.001
			-1.47	-0.39	P<0.001
	Vibegron 50mg	Incontinence episodes/day	-1.10	-	-
			-1.40	-0.30	P=0.001
			-1.53	-0.43	P<0.001
		Nocturia episodes/day	-0.47	-	-
			-0.58	-0.11	P=0.016
			-0.62	-0.16	P=0.001
	Vibegron 100mg	Voided volume/ micturition (mL)	7.80	-	-
			33.55	25.76	P<0.001
			29.96	22.16	P<0.001

[A]95% Confidence interval

placebo (see table 3 for results). For quality-of-life assessment, satisfy criteria in vibegron 50mg and 100mg group was statistically significantly higher (90.8%, 91.6%, respectively; p<0.001) than those in placebo group (76.2%), and very much satisfied was also higher in vibegron 50mg and 100mg group (59.5%, 62.0%, respectively; p<0.001) vs placebo (37.1%).[15]

Adverse Effects and Precautions

Unlike mirabegron, vibegron was not associated with clinically significant changes in blood pressure.10,11 Vibegron also did not show an effect of prolonging the QT interval to any clinically relevant extent with a single dose that is 5.3 times the approved recommendation dose.[10]

The most frequent adverse effects of vibegron vs placebo from the EMPOWUR trial were headache (4% vs 2.4%), nasopharyngitis (2.8% vs 1.7%), diarrhea (2.2% vs 1.1%), nausea (2.2% vs 1.1%), and upper respiratory tract infection (2.0% vs 0.7%).[13] Phase IIb trial has shown the incidence of anticholinergic adverse effects such as dry mouth was higher in tolterodine group compared to vibegron group.[14] Post marketing reported adverse effects are listed as urinary retention, pruritus, rash, drug eruption, eczema, and constipation.[10]

Dosage and Administration

Vibegron is currently available as an oval, light green, film-coated tablet.[10] The recommended dosage is vibegron 75 mg orally once daily with or without food and should be taken with a glass of water. Crushed tablets mixed with tablespoonful (15mL) of applesauce did not have a significant difference in achieving Tmax compared to the intact tablet. Thus, vibegron can be crushed for patients who cannot swallow the tablet and the crushed tablet can be mixed with a tablespoon (approximately 15 mL) of applesauce and taken immediately with a glass of water.[10]

Drug Interactions

Vibegron is a substrate of CYP3A4 and P glycoprotein (P-gp), however no significant differences in vibegron pharmacokinetics were observed with concomitant use of ketoconazole (P-gp and strong CYP3A4 inhibitor), diltiazem (P-gp and moderate CYP3A4 inhibitor), rifampin (strong CYP3A4 inducer), or tolterodine.10 The concomitant use of digoxin and vibegron has increased digoxin serum concentration, therefore avoiding the concomitant use of these two agents or monitoring the serum digoxin concentration to titrate digoxin dose to its desired clinical effect is required.[10]

Cost

Pharmacotherapies that have generic availability such as oxybutynin (oral), tolterodine, and trospium are covered by government provided insurances as tier two or three. Brand only agent, mirabegron, was also covered by Medicare as tier 3 drug. The average retail price of anticholinergic agents, such as oxybutynin ER 10mg 30 tablets, tolterodine 2mg 60 tablets, and trospium 20mg 60 tablets are $82.45, $174.27, and $149.75. Mirabegron which is in the same drug class as vibegorn has retail price as $497.10 for mirabegron 50mg 30 tablets and the coupon discounted price without the insurance is $407.70.

Clinical Implications

The main phase III trial for FDA approval, EMPOWUR trial, was a well-structured randomized placebo- and active- controlled double-blinded clinical trial. The sample size (n=1,518) was large enough to reduce sampling bias and randomized and blinded part were well conducted to reduce the selection bias. The use of tolterodine as an active comparator improved the internal validity of the trial due to its common use in the treatment of OAB.[16] The demographics of this trial included mostly elderly patients (average age 61-63), and female (approximately 85%) which is in line with commonly affected populations and thus increased the external validity.[5,13] Since the current guideline states that there is no cure for OAB, the pharmacotherapy is focused on symptom improvement.[3] Therefore, the primary and secondary endpoints (micturition, UUI episodes, urgency, and average volume voided/micturition) are all well suited for OAB patients to assess their disease state and observe the clinical improvement over time.[13] Furthermore, phase III trials have shown patient's quality of life improved with vibegron better than placebo with statistic significant result.[15] Categorizing and randomizing wet and dry OAB by using this diary make this study to have more accurate result of UUI. Majority of population in EMPOWUR trial was Caucasian (about 80%) and African American (about 15%). On the other hand, phase III trial conducted in Japan with majority of Asian population has shown a statistically significant efficacy result with vibegron group compared to placebo.[15] Thus, the efficacy of vibegron compared to placebo was proven in these three populations with the strong clinical evidence support.

There are potential biases present in these trials. All three trials were funded and supported by the manufacturer, Urovant Science, which could induce a conflict of interest.[13-15] Phase III trial from Japan and EMPOWUR trial had unequal population distribution to its active comparator group and this can impact to the result of the comparison in between intervention group and active comparator group.[13,15] It is unclear about the utility of including the imifenacin group in the Japan trial as there is a lack of detail included in the trial regarding results from this group.[15] The results from EMPOWUR trial were measured by intention to treat analysis with dropout rate less than seven percent. There were 1,463 patients contributed to data and 1,373 completed the trial, but the drop-out rate was very low and also similar throughout the all groups, so the attrition bias was less likely concerned.[13] The measurement for micturition, number of urgency episodes, and volume voided per micturition was done at the best by adequately training patients regarding using the bladder diary before entering this trial, however this subjective measure is the limitation of this study.[13-15]

Vibegron group in all three trials has consistently shown its statistically significant superiority result against placebo by the primary endpoint. The primary endpoint for these three trials were all the change in mean micturition per day from baseline to

Table 4 | Common Vibegron Adverse Effects[10]

Adverse Effect	Incidence Rate
Headache	4.0%
Nasopharyngitis	2.8%
Diarrhea	2.2%
Nausea	2.2%
Upper Respiratory Tract Infection	2.0%

week eight (phase IIb), or week 12 (EMPOWUR, and phase III – Japan).[13-15] Antimuscarinic (anticholinergic) agents have been prescribed as the first-line pharmacologic OAB treatment for many years after non-pharmacological therapy.[17] In addition, the concomitant use of vibegron and antimuscarinic agent, such as tolterodine ER, has been suggested to be more efficacious than tolterodine ER alone by Phase IIb trial having all secondary endpoints favoring concomitant arm group with statistically significant results.[14] Therefore, the concomitant use of vibegron and antimuscarinic agent to optimize treatment is feasible.[14]

In general, the limitation of antimuscarinic agents use and its efficacy is due to its side effects such as dry mouth, constipation, and dizziness.[18] In addition, long term use of antimuscarinic drug for OAB treatment in elderly population was associated in the increased risk of cognitive impairment and dementia.19 Therefore, the AUA guideline recommends the use of beta-3-adrenergic receptor agonist agent in patients with unacceptable adverse events with one anti-muscarinic agent.[3] Vibegron also has shown less incidence of antimuscarinic adverse events, such as dry mouth, compared to tolterodine ER.[13] The biggest concern of using mirabegron is hypertension, so it is essential to monitor patient's blood pressure regularly while they are on mirabegron.[12,20] Plus, the use of mirabegron in patients with systolic blood pressure over 180 and diastolic blood pressure over 120 is not recommended.[12] In contrast, any of clinical trials of vibegron have not shown adverse drug reactions such as hypertension, heart failure, or acute coronary syndrome by having no effect in change in blood pressure or QTc interval.[10] Head to head trials comparing cardiovascular outcomes between vibegron and mirabegron are not currently available. However, vibegron is possible to use in hypertensive patients without worrying of increase in blood pressure unlike mirabegron while avoiding side effects of antimuscarinic agent. Patients on vibegron group in EMPOWUR trial had statistically significant primary and secondary endpoint results with a set dose, 75mg once daily.[13] Unlike mirabegron which may need a dose titration, vibegron can be used without the titration and achieve a desired clinical effect.[10,12]

The two-year large cohort study conducted by Michael C et al stated that the mean time to treatment failure of antimuscarinic agent for OAB treatment was around five to six months and many patients ended up without the effective pharmacotherapy.[21] The superiority of vibegron compared to placebo was shown in EMPOWUR trial as early as week two with the statistically significant difference in its primary endpoint favoring vibegron and the difference was maintained at all subsequent exploratory time points whereas its active comparator tolterodine 4mg ER has failed to show this.[13] Therefore, two weeks efficacy of vibegron can avoid the treatment failure of OAB and re-challenging with vibegron is possibly beneficial for patients who failed with antimuscarinic agents.

Metabolism with p450 enzyme, CYP3A4, with this drug takes a minor role, thus the lack of important drug interactions is the strength of this drug.[10] Digoxin is the only exception, so the concomitant use of digoxin and vibegron requires monitoring digoxin level or avoiding to use these agents together. Lastly, vibegron is currently trying to expand its indications, OAB in men with benign prostate hyperplasia (BPH) currently on phase III trial, and irritable bowel syndrome associated pain on phase II trial. Once these two trials are approved, the utility of vibegron will expand much broader.

Cost remains an issue for vibegron, as both manufacturer pricing and formulary coverage have not been established. Until more head-to-head trials are available, clinicians should be able to appropriately assess patients with their clinical knowledge and judgement for them to receive maximum benefit from the pharmacotherapy while the cost makes sense.

Conclusion

Gemtesa® (vibegron) is a beta-3-adrenergic agonist with the FDA approval for the treatment of OAB. This therapy has shown statistically significant and clinically meaningful improvement in OAB symptoms including reduction in micturition per day and/or reduction in UUI episodes when compared to placebo. It offers a generally tolerable adverse effect profile as there is no anticholinergic side effects or no effect on hypertension. However, there are no current trials directly comparing this therapy to those already FDA approved for OAB so determining its place in therapy requires further study.

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Drug Updates: New Indications and Dosage Forms June 2021

Zegalogue® (dasiglucagon) Autoinjector and Syringe
New Formulation: Treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and older

Nextstellis® (drospirenone and estetrol) Oral Tablet
New Formulation: Indicated for use by females of reproductive potential to prevent pregnancy

Lybalvi® (olanzapine/samidorphan) Oral Tablet
New Combination: Treatment of schizophrenia and bipolar I disorder in adults; for use as monotherapy or adjunctive treatment

Brexafemme® (ibrexafungerp) Oral Tablet
New Formulation: Triterpenoid antifungal indicated for treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis

Aduhelm® (aducanumab) Injection
New Formulation: Novel treatment of Alzheimer's disease administered via intravenous infusion

Azstarys® (serdexmethylphenidate and dexmethylphenidate) Oral Capsule
New Formulation: Central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older

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