Brand Name: Gemtesa

Generic: Vibegron

Manufacturer[1]: Urovant Sciences, Inc.

Drug Class[2-5]: Beta-3 adrenergic receptor agonist (beta-3 AR)

Uses:

Labeled Uses[1-5]**:** Treatment of overactive bladder (OAB) with symptoms of urgency, urinary incontinence and urinary frequency in adults

Unlabeled Uses[2,4]**:** N/A

Mechanism of Action[2-5]**:**

Selective human beta-3 adrenergic receptor agonist. Activation of this receptor increases bladder capacity by relaxation of the detrusor smooth muscle during bladder filling.

Pharmacokinetics[1-5]**:**

Tmax: 1-3 hours

Vd: 6,304 L

T ½ : 30.8 hours

Clearance: Not reported

Protein Binding: 50%

Bioavailability: Not reported

Metabolism[2-5]**:** Metabolism plays a minor role in the elimination of vibegron, predominately by CYP3A4.

Elimination[2-5]**:** 59% of the dose was found in the feces (54% unchanged) and 20% in urine (19% unchanged).

Efficacy[6-8]**:**

Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR. *J Urol*. 2020;204(2):316-324.

Study design: Randomized, double-blind, placebo and active control

Description of Study: *Methods*- This study consisted of a 1 to 5-week screening period with a 28-day washout, a 2-week single-blind (patient) placebo run-in, and a 12 week double-blind (patients, investigators, sponsor) period. Patient reported outcomes were recorded in a voiding

diary and were assessed at baseline and at weeks 2, 4, 8, and 12. Patients were randomized to 75 mg vibegron, placebo, or 4 mg tolterodine ER. There were 2 predefined co-primary end points. The first is change from baseline to week 12 in the average daily number of micturitions and the second was change from baseline to week 12 in the average daily number of urge urinary incontinence (UUI) episodes. *Outcome Results*- 1,518 patients were randomized at 199 study sites. At 12 weeks, the least-squares (LS) mean change in micturition frequency among 492 patients in the vibegron group was -1.8 episodes per day, compared with -1.3 among 475 patients in the placebo group, a LS mean difference of -0.5 (95% CI -0.8, -0.2; p <0.001). For tolterodine the LS mean 12-week change among 378 patients was -1.6, a LS mean difference of -0.3 from placebo (95% CI -0.6, 0.1; p=0.0988). A statistically significant decrease in adjusted mean change for vibegron vs placebo was achieved by week 2 and was maintained at all subsequent exploratory time points. At 12 weeks the LS mean change in UUI episode frequency among 383 patients in the vibegron group was –2.0 episodes per day, compared with –1.4 among 372 patients in the placebo group, a LS mean difference of –0.6 (95% CI –0.9, –0.3; p <0.0001). For tolterodine the LS mean 12-week change among 286 patients was –1.8, a LS mean difference of –0.4 from placebo (95% CI –0.7, –0.1; p=0.0123). A statistically significant decrease in adjusted mean change for vibegron vs placebo was already achieved by the week 2 exploratory end point and was maintained at all subsequent time points.

Limitations: Potential limitations of the present trial include the 12-week duration. However, patients in the present trial could roll over into a 52-week extension study. Moreover, the long-term extension, quality of life and other measures will be reported in future publications but were not reported in this publication. The manufacturer provided study support for the trial which could have introduced bias into the study.

Conclusion: In the EMPOWUR phase III study 75 mg vibegron provided statistically significant improvements in OAB symptoms, including the co-primary end points of reduction in daily micturitions and UUI episodes at 12 weeks, and the important secondary end points of reduction in daily urgency episodes and increase in volume voided per micturition. Statistically significant efficacy began by week 2 and was maintained through week 12. Vibegron was generally safe with AE rates comparable with those for placebo, including the incidence of hypertension.

Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a Novel Potent and Selective β3-Adrenoreceptor Agonist, for the Treatment of Patients with Overactive Bladder: A Randomized, Double-blind, Placebo-controlled Phase 3 Study. *Eur Urol*. 2018;73(5):783-790.

Study Design: Randomized, double-blind placebo controlled, parallel phase 3 study

Description of Study: *Methods:* This was a multicenter, randomized, four-arm, parallel-group, placebo-controlled phase 3 study in patients with OAB. Imidafenacin, an anticholinergic mainly used in Asia, was used as an active control. The study was conducted at 109 sites in Japan from July 2015 to June 2016. Patients with OAB symptoms for ≥6 mo who met the eligibility criteria entered a 2-wk placebo run-in phase. Once eligibility was confirmed at the end of the run-in

phase, patients were randomly assigned in a 3:3:3:1 ratio to one of the following four treatment groups: vibegron (50 mg or 100 mg once daily), placebo, or imidafenacin (0.1 mg twice daily). The assigned study drug was administered orally after a meal for 12 wk. *Outcome Results:* Treatment with vibegron 50 mg and 100 mg significantly improved the primary and secondary efficacy variables, compared with placebo. For the primary endpoint, the change in LS mean of micturitions/d at wk 12 from baseline was −2.08 in the vibegron 50 mg group, −2.03 in the vibegron 100 mg group, and −1.21 in the placebo group, respectively. The estimated difference (95% confidence interval) in mean micturitions/d between the vibegron groups and placebo was −0.86 (−1.12, −0.60) for vibegron 50 mg ($p < 0.001$) and −0.81 (−1.07, −0.55) for vibegron 100 mg ($p < 0.001$). With respect to the secondary endpoints (number of daily urgency episodes, urgency incontinence episodes, incontinence episodes, and nocturia episodes, and voided volume/micturition), vibegron 50 mg and 100 mg showed significant improvements in the LS mean changes at wk 12 from baseline, compared with placebo.

Limitations: The proportions of elderly patients and male patients in this study were lower than those in real world. Although imidafenacin was used as an active control, no statistical analysis was performed between vibegron and imidafencin. Additionally, the comparison to imidfencin may not generalize to areas in which this agent is not generally used or available. The treatment period of 12 weeks was too short to evaluate the real-world effects of vibegron because vibegron might be used for longer than 12 weeks.

Conclusion: Vibegron 50 mg and 100 mg once daily for 12 wk provided significantly greater efficacy over placebo in the treatment of Japanese patients with OAB. Vibegron was generally well tolerated and no major safety issues were identified.

Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) Administered Once Daily as Monotherapy or Concomitantly with Tolterodine in Patients with an Overactive Bladder: A Multicenter, Phase IIb, Randomized, Double-blind, Controlled Trial. *Eur Urol*. 2019;75(2):274-282.

Study Design: Multicenter, randomized, double-blind, controlled trial

Description of Study: *Methods:* For each part of the trial, patients were stratified as OAB-wet or OAB-dry at randomization (visit 3) using an interactive response technology system. In part 1, patients were equally randomized to receive one of seven treatments. Patients received once-daily vibegron (3 [V3], 15 [V15], 50 [V50], or 100 [V100] mg), tolterodine ER 4 mg (TER4), or placebo for 8 weeks or concomitant V50/TER4 for 4 weeks, and then V50 for 4 weeks. Vibegron dose selection for part 2 was based on the interim results from part 1. In part 2, patients were randomized 2:2:2:1 to receive once-daily V100, TER4, V100/TER4, or placebo for 4 weeks. Patients could take the study medications with or without food. *Outcome Results:* In part 1, vibegron (V50 and V100) monotherapy resulted in a significant dose-related decrease in LSM daily number of micturitions from baseline to that at week 8 versus placebo (difference in LSM: −0.64 and −0.91, respectively; both $p < 0.05$). Treatment with V50 (part 1) or V100 (parts 1 and 2) also significantly decreased LSM daily number of micturitions from baseline to week 4 (all p

< 0.05). Furthermore, patients treated with V50 or V100 experienced significant decreases in LSM daily number of urgency episodes from baseline through week 8 (part 1). OAB-wet patients exhibited significant reductions in LSM daily number of urge incontinence episodes from baseline to week 8 versus placebo in all but one active treatment group (all except V3, $p < 0.05$). Furthermore, OAB-wet patients treated with V15, V50, or V100 exhibited a significant decrease in LSM daily number of total incontinence episodes from baseline to week 8 versus placebo.

Limitations: Limitations of this trial include the relatively short treatment duration (up to 8 wk); however, further results from the 1-yr extension of this study will provide additional long-term efficacy and safety assessment. Additionally, this trial was not designed to enable a direct statistical comparison of the magnitude of efficacy benefit for vibegron versus TER4.

Conclusion: The efficacy and safety of once-daily oral vibegron in treating OAB, with or without incontinence, was clearly demonstrated in this phase IIb trial. Vibegron was well tolerated, and the observed efficacy results support further study of vibegron for the treatment of OAB.

Contraindications (1,2,3,4,5): Vibegron is contraindicated in patients who have a known hypersensitivity to any component of the formulation.

Precautions (1,2,3,4,5):

Bladder outlet obstruction: Vibegron should be used with caution in patients with bladder outlet obstruction. The risk of urinary retention may be increased in these patients. Monitor patients for signs and symptoms of urinary retention and discontinue vibegron in patients who develop urinary retention.

Anticholinergic Medications: Vibegron should be used with caution in patients taking anticholinergic medications for the treatment of OAB. The risk of urinary retention may be increased in these patients. Monitor patients for signs and symptoms of urinary retention and discontinue vibegron in patients who develop urinary retention.

Lactation: There is no data on the presence of vibegron in human breast milk, however, when given postnatally to an animal it was found in the animal's milk. When a drug is found in animal milk, it is likely that the drug will be found in human milk. The developmental and health benefits of breastfeeding should be considered as well as the mother's clinical need for vibegron. Consider any potential adverse effects on the breastfed infant or from the underlying maternal condition.

Children: The safety and effectiveness of vibegron in patients less than 18 years old have not been studied. Therefore, use of vibegron in these patients is not recommended.

End-Stage Renal Disease: Vibegron is not recommended in patients with end-stage renal disease or renal failure (eGFR less than 15). Dosage adjustments for patients with mild, moderate, or severe renal impairment are not necessary (eGFR 15-90).

Hepatic Disease: Vibegron is not recommended for use in patients with severe hepatic disease or impairment. Dosage adjustments for patients with mild to moderate hepatic impairment are not necessary.

Pregnancy: There is no available data determining fetal risk in pregnant patients taking vibegron. Consider the risks and benefits of using this medication before prescribing to pregnant patients.

Adverse Effects (1,2,3,4,5):

Occurring in >10% of patients

None.

Occurring in >1% to <10% of patients

Endocrine and Metabolic

Hot Flashes (<2%)

Gastrointestinal

Constipation (<2%)

Diarrhea (2%)

Nausea (2%)

Xerostomia (<2%)

Genitourinary

Urinary Retention (<2%)

Nervous System

Headache (4%)

Respiratory

Naso-pharyngitis (3%)

Upper Respiratory Tract Infection (2%)

Drug Interactions (1,2,3,4,5):

Digoxin

Vibegron may increase serum concentrations of digoxin. Measure serum digoxin concentrations before starting Vibegron.

Dosing/Administration (1,2,3,4,5):

Adult Dosing

Vibegron is dosed at one 75 mg tablet by mouth once daily for the treatment of OAB with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency. Can be given with or without food. Swallow the tablet whole with water or crush the tablets and mix with applesauce.

Pediatrics

The use of vibegron in patients less than 18 years of age is not recommended.

Elderly

Vibegron is dosed at one 75 mg tablet by mouth once daily for the treatment of OAB with symptoms of urge urinary incontinence, urinary urgency, and urinary frequency. Can be given with or without food. Swallow the tablet whole with water or crush the tablets and mix with applesauce.

Renal Impairment

No dosage adjustment is needed for patients with an eGFR of 15 or more. The use of vibegron in patients with eGFR less than 15 is not recommended.

Hepatic Impairment

No dosage adjustment is needed for patients with mild to moderate hepatic impairment. The use of vibegron in patients with severe hepatic impairment is not recommended.

Conclusion: Vibegron is an effective and safe treatment option for patients with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. More studies need to be done to evaluate vibegron's efficacy with longer durations. Also, vibegron should be compared to active controls with similar mechanisms of action (mirabegron). In the studies listed above, some included an active comparator (mainly tolterodine), but the investigators did not statistically compare the active comparator with vibegron. Vibegron does have less drug interactions associated with use compared to mirabegron which might lend some clinical advantage to vibegron compared to mirabegron. Many resources suggest a trial of other agents to treat OAB prior to initiating a beta-3 adrenergic receptor agonist medication such as mirabegron or vibegron. Thus, vibegron's place in therapy may be limited to patients who have failed other therapies or have contraindications to other OAB therapies. Overall, the drug seems to be effective and safe and does provide an additional alternative when treating OAB.

Recommended References:

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4. Vibegron. In: DRUGDEX System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: June 3, 2021.

5. Vibegron Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: June 3, 2021.

6. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR. J Urol. 2020;204(2):316-324.

7. Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a Novel Potent and Selective β3-Adrenoreceptor Agonist, for the Treatment of Patients with Overactive Bladder: A Randomized, Double-blind, Placebo-controlled Phase 3 Study. Eur Urol. 2018;73(5):783-790.

8. Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) Administered Once Daily as Monotherapy or Concomitantly with Tolterodine in Patients with an Overactive Bladder: A Multicenter, Phase IIb, Randomized, Double-blind, Controlled Trial. Eur Urol. 2019;75(2):274-282.

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