# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 213006Orig1s000

# OFFICE DIRECTOR MEMO

Office Director Decisional Memo

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Hylton V. Joffe, M.D., M.M.Sc. |
| **Subject** | Office Director Decisional Memo |
| **NDA/BLA # and Supplement #** | NDA 213006 |
| **Applicant** | Urovant Sciences GMBH |
| **Date of Submission** | December 26, 2019 |
| **PDUFA Goal Date** | December 26, 2020 |
| **Proprietary Name** | Gemtesa |
| **Established or Proper Name** | Vibegron |
| **Dosage Form(s) / Strength** | 75 mg tablets |
| **Applicant Proposed Indication(s)/Population(s)** | For the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency |
| **Action:** | Approval |
| **Approved Indication(s)/Population(s)** (if applicable) | For the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Clinical Review | Debuene Chang, Mark Hirsch |
| Statistical Review | Jia Guo, Daphne Lin |
| Pharmacology Toxicology Review | Laurie McLeod-Flynn, Kimberly Hatfield, Mukesh Summan |
| OPQ Review | Friedrich Burnett, Donna Christner, Michael Theodorakis, Moo-Jhong Rhee, Wendy Wilson-Lee, Zhao Wang, Jean Tang, Kalpana Paudel, Vidula Kolhatkar, Marquita Burnett, Mark Seggel, James Laurenson |
| Clinical Outcome Assessment Staff | Parima Ghafoori, Selena Daniels, Elektra Papadopoulos |
| Clinical Pharmacology Review | Lin Zhou, Junshan Qiu, Jingyu Yu, Yanhui Lu, Shirley Seo |
| OPDP | Elvy Varghese, Matthew Falter |
| OSI | Ling Yang, Min Lu, Kassa Ayalew |
| CDTL Review/Summary Review | Mark Hirsch, Audrey Gassman |
| OSE/DMEPA | Justine Kalonia, Denise Baugh, Briana Rider, Danielle Harris |
| OSE/DRISK | Theresa Ng, Laura Zendel, Cynthia LaCivita |
| Division of Cardiology and Nephrology | Yu Yi Hsu, Dalong Huang, Raman Baweja, Nan Zheng, Michael Li, Lars Johannesen, Fortunato Senatore, Christine Garnett, Preston Dunnmon, Norman Stockbridge |
| Office of Medical Policy/Division of Medical Policy Programs | Lonice Carter, Elvy Varghese, Sharon Williams, LaShawn Griffiths |

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DRISK=Division of Risk Management

## 1. Benefit-Risk Assessment Framework

**Benefit-Risk Integrated Assessment**

Patients with overactive bladder typically have urinary urgency (the need to urinate immediately), urinary frequency (an increased frequency of urination), and nocturia, with about one-third of patients also having urge urinary incontinence (involuntary leakage of urine associated with the need to urinate immediately). While not life-threatening, these chronic symptoms affect quality of life. There are several antimuscarinic medications and one beta-3-adrenergic receptor agonist (mirabegron) approved as second-line therapy for the treatment of overactive bladder, with behavioral therapy such as weight loss and fluid management recommended as first-line treatment.

Vibegron (tradename Gemtesa) is the second-in-class beta-3-adrenergic receptor agonist developed for overactive bladder. Activation of beta-3-adrenergic receptors in the bladder wall results in bladder detrusor muscle relaxation and reduced spontaneous contractions. The Applicant is seeking approval of 75 mg tablets taken orally once daily.

Substantial evidence of effectiveness for the 75 mg once daily dose was established in a 12-week, randomized, double-blind, placebo-controlled trial predominantly conducted in the United States (Study 3003) together with confirmatory evidence from two other randomized, double-blind, placebo-controlled trials that tested different doses of vibegron (a 12-week trial in Japan that assessed 50 mg and 100 mg once daily and an 8-week, dose-finding phase 2 trial that included 50 mg and 100 mg once daily dosing regimens). These two trials did not test the 75 mg once daily dose; however, their consistent findings on the symptoms of overactive bladder, including with their 50 mg dosing regimen provides confirmatory evidence of effectiveness for the 75 mg dose proposed for marketing in the United States.

In Study 3003, patients at baseline had on average about 11 urinary episodes per day, about 3.5 urge urinary incontinence episodes per day, and about 8 urgency episodes per day. Compared to baseline and placebo, at week 12 of treatment, the vibegron patients had on average 0.5 fewer urinary episodes per day (95% confidence interval 0.2 to 0.8), 0.6 fewer urge urinary incontinence episodes per day (95% confidence interval 0.3 to 0.9), and 0.7 fewer urgency episodes per day (95% confidence interval 0.2 to 1.1). Over a course of a month, this would, on average, translate to about 15 fewer urinary episodes, 18 fewer urge urinary incontinence episodes and 21 fewer urgency episodes. Using anchor-based methods with data from this trial, it was estimated that at least a 90% reduction in urge urinary incontinence and at least a 60% reduction in urgency may be clinically meaningful to the trial participants. Thirty five percent of vibegron-treated patients and 24% of placebo-treated patients had at least 90% reduction in urge urinary incontinence, and 34% of vibegron-treated patients and 28% of placebo-treated patients had at least 60% reduction in urgency. While the mean changes with vibegron are modest, these changes are consistent with those seen with other approved overactive bladder medications, including mirabegron, whose effectiveness was endorsed at a 2012 public advisory committee meeting. In addition, the

findings are not only statistically significant, but show that some vibegron-treated patients can obtain considerable improvement in their symptoms.

The findings for men and non-whites are less conclusive for urge urinary incontinence because of small subgroups and baseline imbalances in urge urinary incontinence episodes. Nonetheless, the comparable effects in the larger subgroup of men and non-whites assessed for urinary frequency are reassuring.

Vibegron's safety profile has been sufficiently characterized in the pre-approval database with up to 52 weeks of safety data that meets long-term patient exposures recommended for drugs that treat chronic, non-life-threatening conditions. These safety data are supplemented with data from the 100 mg dose evaluated in the Japanese clinical development program as well as post-marketing experience in Japan. Some of the risks are tolerability issues (e.g., headache, nausea) but others could be more significant (hypersensitivity reactions, urinary retention, a drug-drug interaction with digoxin). Hypersensitivity reactions (e.g., rash, drug eruptions) were identified in Japan's postmarketing experience. Urinary retention was reported in 0.6% of vibegron-treated patients vs. 0.4% of placebo-treated patients in Study 3003 and identified in Japan's postmarketing experience. Urinary retention is a well-known infrequent risk with all approved overactive bladder medications, particularly in patients with bladder outlet obstruction and those who use antimuscarinic medications and can increase the risk for urinary tract infection and the need for temporary catheterization. Notably, vibegron does not cause clinically meaningful increases in blood pressure – a side effect seen with mirabegron, the other beta-3-adrenergic receptor agonist approved for overactive bladder.

From a drug-drug interaction standpoint, vibegron increases digoxin exposures with concomitant administration. Although the increase is modest it could be clinically significant because digoxin is a narrow therapeutic drug. No dosage adjustment is required for vibegron based on intrinsic or extrinsic factors, although vibegron is not recommended for patients with end-stage renal disease or severe hepatic impairment because it was not studied in those populations.

After review of the safety database, we determined that vibegron's risks can be adequately mitigated with labeling alone and that no postmarketing required studies or trials are needed for safety. Because of the infrequent reports of hypersensitivity reactions in Japan's postmarketing experience, the labeling will include a contraindication in patients with a prior hypersensitivity reaction to vibegron or its ingredients. The infrequent risk of urinary retention – which is a well-known side effect of all overactive bladder medications – can be adequately mitigated with a Warning and Precaution like the approach used with other overactive bladder medications. Labeling will note the increase in risk with bladder outlet obstruction, to monitor for signs and symptoms of urinary retention, and to discontinue vibegron if urinary retention occurs. The risk for increased digoxin concentrations with coadministration can also be mitigated with labeling, which is the typical approach for such interactions. Labeling will recommend periodic monitoring of digoxin concentrations and adjusting the

digoxin dose accordingly.

In summary, the benefits with vibegron are comparable to those of other approved treatments for overactive bladder and the risks are manageable with labeling alone. Vibegron provides another useful treatment option for overactive bladder without the blood pressure increases seen with mirabegron. Some patients will have considerable improvements in their symptoms with vibegron and because overactive bladder is a symptomatic condition, those that do not can decide to discontinue the medication.

**Benefit Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Patients with overactive bladder typically have urinary urgency (the need to urinate immediately), urinary frequency (a need to frequently urinate), and nocturia, with about one-third of patients also having urge urinary incontinence (involuntary leakage of urine associated with the need to urinate immediately).<br>• The prevalence of overactive bladder increases with age, affecting about one-third of those 75 years of age and older.<br>• The symptoms of overactive bladder adversely impact quality of life. | Although not life-threatening, overactive bladder is a chronic condition that becomes more prevalent with advancing age and can significantly impact quality of life. |
| **Current Treatment Options** | • First-line therapy is behavioral therapy including weight loss, pelvic floor therapy, and fluid management.<br>• Second-line therapy includes an antimuscarinic medication (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) and/or a beta 3-adrenergic receptor agonist (mirabegron). These therapies are modestly effective, although some patients can have considerable symptomatic improvement. Antimuscarinic medications can cause dry mouth, constipation, blurred vision, urinary retention, dyspepsia, and possibly impaired cognitive function, and are contraindicated in patients with uncontrolled narrow angle glaucoma, gastric retention, and urinary retention. Mirabegron can increase blood pressure and can cause urinary retention, angioedema, urinary tract infections, and headache.<br>• Third-line options include botulinum toxin intravesical injections, peripheral nerve stimulation, or neuromodulation with surgical implantation of an | There are a variety of treatment options for overactive bladder, but they are generally modestly effective or invasive. There is a need for more efficacious and safe medication alternatives to treat the symptoms of overactive bladder.<br><br>Mirabegron is the only FDA-approved beta 3-adrenergic receptor agonist for the treatment of overactive bladder. It can cause clinically relevant increases in blood pressure. Approval of another beta 3-adrenergic receptor agonist that does not have a blood pressure effect, would be a useful addition to the treatment |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | electrical stimulator. These invasive treatments are reserved for patients who do not adequately respond or cannot tolerate the first- and second-line therapies. | armamentarium. |
| **Benefit** | • The Applicant is seeking approval of vibegron (tradename Gemtesa) 75 mg tablets taken orally once daily.<br>• Substantial evidence of effectiveness for vibegron 75 mg once daily was established in a 12-week, randomized, double-blind, placebo-controlled trial predominantly conducted in the United States (Study 3003) together with confirmatory evidence from two other randomized, double-blind, placebo-controlled trials that tested different doses of vibegron (a 12-week trial in Japan that assessed 50 mg and 100 mg once daily and an 8-week, dose-finding phase 2 trial that included 50 mg and 100 mg once daily dosing regimens). These two trials did not test the 75 mg once daily dose; however, their consistent findings on the symptoms of overactive bladder, including with their 50 mg dosing regimen provides confirmatory evidence of effectiveness for the 75 mg dose proposed for marketing in the United States.<br>• In Study 3003, patients at baseline had on average about 11 urinary episodes per day, about 3.5 urge urinary incontinence episodes per day, and about 8 urgency episodes per day. Compared to baseline and placebo, at week 12 of treatment, the vibegron patients had on average 0.5 fewer urinary episodes per day (95% confidence interval 0.2 to 0.8), 0.6 fewer urge urinary incontinence episodes per day (95% confidence interval 0.3 to 0.9), and 0.7 fewer urgency episodes per day (95% confidence interval 0.2 to 1.1). Over a course of a month, this would, on average, translate to about 15 fewer urinary episodes, 18 fewer urge urinary incontinence episodes and 21 fewer urgency episodes. | Vibegron modestly reduces urinary frequency, urinary urge incontinence, and urgency in patients with overactive bladder. The mean changes are small, but these changes are consistent with those seen with other approved overactive bladder medications, including mirabegron, another approved beta-3 receptor agonist whose effectiveness was endorsed at a public advisory committee meeting. In addition, the data show that some vibegron-treated patients can obtain considerable improvement in their symptoms. Because overactive bladder is a symptomatic condition, patients will be able to gauge for themselves whether they are experiencing enough benefit with vibegron.<br><br>The findings for men and non-whites are less conclusive for urge urinary incontinence because of small subgroups and baseline imbalances in urge urinary incontinence episodes. Nonetheless, the comparable effects in the larger subgroup of men and non-whites assessed for urinary frequency are reassuring. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • Using anchor-based methods with data from Study 3003, it was estimated that at least a 90% reduction in urge urinary incontinence and at least a 60% reduction in urgency may be clinically meaningful to the trial participants. Thirty five percent of vibegron-treated patients and 24% of placebo-treated patients had at least 90% reduction in urge urinary incontinence, and 34% of vibegron-treated patients and 28% of placebo-treated patients had at least a 60% reduction in urgency.<br>• About 15% of enrolled patients in Study 3003 were men and 22% of the enrolled patients were non-white. The review team agreed with enrolling a smaller proportion of men in the trial because it is difficult to identify men whose symptoms are due to overactive bladder rather than benign prostatic hyperplasia, which is common in older men and not the indication being evaluated in the trial. For urinary frequency, the reductions in men and non-white patients appeared comparable to those in women and whites. However, a trend for urge urinary incontinence was not clearly seen among men and non-whites, with point estimates for the treatment difference around zero and wide confidence intervals. This subgroup analysis was limited by small sample sizes (because it required patients to have urge urinary incontinence at baseline) and by an imbalance in urge urinary incontinence episodes at baseline, yielding inconclusive subgroup results and limiting conclusions. | |
| **Risk and Risk Management** | • Vibegron's risks include:<br>o Hypersensitivity reactions (e.g., rash, drug eruptions), identified in Japan's postmarketing experience.<br>o Urinary retention, reported in 0.6% of vibegron-treated patients vs. 0.4% of placebo-treated patients in Study 3003, and identified in Japan's postmarketing experience. This is a well-known infrequent | Vibegron's safety profile has been sufficiently characterized in the pre-approval database and supplemented with post-marketing experience in Japan. No required postmarketing studies or trials are needed for safety. Several risks are tolerability issues (e.g., headache, nausea) but others could be more significant (hypersensitivity reactions, urinary retention, a |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | risk with all approved overactive bladder medications that is increased in patients with bladder outlet obstruction. Urinary retention can increase the risk for urinary tract infection and the need for temporary catheterization.<br><br>o Vibegron's most common adverse reactions include headache, urinary tract infection, nasopharyngitis, diarrhea, nausea, and upper respiratory tract infection.<br><br>o Vibegron increases digoxin exposures with concomitant administration. Although the increase is modest it could be clinically relevant because digoxin is a narrow therapeutic drug.<br><br>• Vibegron did not cause clinically relevant increases in blood pressure or heart rate on ambulatory blood pressure monitoring. | drug-drug interaction with digoxin). These risks can be adequately mitigated with labeling alone. Because of the infrequent reports of hypersensitivity reactions in Japan's postmarketing experience, the labeling will include a contraindication in patients with a prior hypersensitivity reaction to vibegron or its ingredients. The infrequent risk of urinary retention – which is a well-known side effect of all overactive bladder medications – can be adequately mitigated with a Warning and Precaution like the approach used with other overactive bladder medications. Labeling will note the increase in risk with bladder outlet obstruction, to monitor for signs and symptoms of urinary retention, and to discontinue vibegron if urinary retention occurs. The risk for increased digoxin concentrations with coadministration can also be mitigated with labeling, which is the typical approach for such interactions. Labeling will recommend periodic monitoring of digoxin concentrations and adjusting the digoxin dose accordingly. |

## 2. Further discussion to support regulatory action

### Background

This is the Office Director memorandum for the vibegron (tradename Gemtesa) new drug application. The main issues and their resolution are well-summarized in the discipline reviews and Cross-Discipline Team Leader memorandum (which is cosigned by the deputy division director and serves as the summary review). All review team members and disciplines and the summary review recommend approval, and I agree that the application can be approved. Here I highlight the basis for concluding there is substantial evidence of effectiveness for the 75 mg dose. This dose was studied in only one adequate and well-controlled trial and is the only dose proposed for marketing in the United States. I also provide our reasoning for not proceeding to advisory committee and the basis for some aspects of the final labeling, and summarize the required pediatric postmarketing trial.

### Clinical/Statistical – Efficacy

Substantial evidence of effectiveness for the 75 mg dose is established based on one adequate and well-controlled trial (Study 3003) and confirmatory evidence. Study 3003 was a 12-week, adequate and well-controlled trial conducted predominantly in the United States. This trial was randomized, double-blind, and placebo-controlled. As discussed in the clinical and statistical reviews and in the summary review, vibegron 75 mg daily demonstrated improvements compared to placebo on the standard co-primary efficacy endpoints for overactive bladder trials – a reduction in the number of daily micturations ($p<0.001$) and a reduction in urge urinary incontinence ($p<0.0001$) – as well as a reduction in urgency ($p=0.002$) and improvements on other secondary endpoints. As discussed in the benefit-risk framework, mean changes compared to placebo were modest but there were patients who had clinically meaningful changes on anchor-based analyses. The improvements on the co-primary efficacy endpoints are consistent with that seen with other approved overactive bladder drugs, including mirabegron, the first-in-class beta-3 receptor agonist approved for overactive bladder.

There are two additional trials that provide confirmatory evidence of effectiveness for the 75 mg dose. The first is Study 301, which was a 12-week, randomized, double-blind, placebo-controlled phase 3 trial that evaluated the efficacy and safety of vibegron 50 mg and 100 mg once daily in Japanese patients with overactive bladder and supported the marketing authorization in Japan. The second trial is Study 008, which was a 2-part, randomized, double-blind, placebo-controlled trial. The first part had an 8-week treatment period that included randomized arms for four vibegron doses (3, 15, 50, and 100 mg) and placebo. Neither trial studied the 75 mg vibegron dose, and there were other notable trial design differences from Study 3003 (e.g., the 8-week duration for Study 008, the Japanese patient population in Study 301). Nonetheless, as discussed in the clinical review the efficacy findings across the trials were consistent, including for the 50 mg dose, which provides confirmatory evidence of effectiveness for the 75 mg dose.

## Advisory Committee Meeting

We did not convene an advisory committee meeting for vibegron. We took mirabegron, the first-in-class beta-3 receptor agonist, to advisory committee prior to its approval. Based on cross-study comparisons, vibegron has similar efficacy to mirabegron (and to the antimuscarinic medications approved for overactive bladder). In addition, vibegron does not have unique safety issues (and in fact, does not have the blood pressure effect seen with mirabegron). Therefore, we determined that there was no need for external expertise to inform the approvability of the application.

## Labeling

I agree with the final labeling, the rationale for which is well-described in the discipline reviews. Here I provide additional rationale for the labeling content decisions that were finalized after the discipline reviews were completed.

- As noted in the Clinical Pharmacology review and labeling, coadministration of vibegron and digoxin (a narrow therapeutic drug and a P-gp substrate) increased the area under the concentration-time curve (AUC) of digoxin by 11% (90% confidence interval of the geometric mean ratio: 1.03-1.19) and increased digoxin maximal concentrations (Cmax) by 21% (90% confidence interval of the geometric mean ratio: 1.09-1.35). Because digoxin is a narrow therapeutic drug, the observed increase in digoxin Cmax warrants labeling regarding coadministration of digoxin and vibegron. Although the mean increase in systemic exposure (AUC) to warfarin (another narrow therapeutic drug) appears larger than the AUC increase seen with digoxin (increased AUC of S-warfarin of 18% and R-warfarin of 17%), the corresponding 90% confidence intervals of the geometric mean ratios for warfarin were within the 0.80-1.25 interval typically used for bioequivalence and this extent of increase in warfarin concentrations did not affect warfarin pharmacodynamics in a published drug-drug interaction study with another drug (Desai A, et al.). Therefore, I agree that no labeling is needed for additional warfarin monitoring with concomitant vibegron administration.

- While the clinical review notes that there have been 47 postmarketing reports of dry mouth and 65 postmarketing reports of dysuria in Japan, we decided not to label these in Section 6.2 given that these are commonly reported adverse events in overactive bladder patients.

- We had asked the Applicant to include a cumulative distribution function plot of urge urinary incontinence episodes to show the cumulative distribution of responses between treatment groups and characterize the treatment effect across the trial population given the modest mean effects. The Applicant noted that other approved overactive bladder products do not include such plots and that those plots are difficult to understand. I do not consider this a valid reason as our labeling practices improve over time and an introductory paragraph could be added to orient the prescriber to the

plot. However, I do agree with another reason provided by the Applicant that the treatment effects seen with vibegron are comparable to those seen with the other approved products. Based on the discussions at the 2012 advisory committee meeting for mirabegron, healthcare providers who would consider prescribing treatments for overactive bladder are expected to be familiar with the extent of improvement seen with these products. Therefore, we did not proceed with these plots in labeling.

**Postmarketing Requirements and Commitments**

As with products intended for the treatment of overactive bladder, the Applicant will be required to conduct a postmarketing required trial in pediatric patients with neurogenic detrusor overactivity under the Pediatric Research Equity Act. The Applicant requested a deferral for patients aged 3 to less than 17 years of age and a partial waiver for patients under 3 years of age (because studies are highly impractical in this younger age group). The milestones were discussed with the Pediatric Review Committee and agreed to by the Applicant and are included in the Approval letter. The protocol will be finalized during the post-approval period.

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

HYLTON V JOFFE
12/23/2020 11:19:06 AM