CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213006Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213006
PDUFA Goal Date	December 26, 2020
OSE RCM #	2019-2648
Reviewer Name	Theresa Ng, PharmD, BCPS
Team Leader	Laura Zendel, PharmD, BCPS
Deputy Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 9, 2020
Subject	Evaluation of Need for a REMS
Established Name	Vibegron
Trade Name	Gemtesa
Name of Applicant	Urovant Sciences
Therapeutic Class	Beta-3 adrenergic agonist
Formulation(s)	75 mg tablet
Dosing Regimen	One tablet orally once daily with or without food

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Gemtasa (vibegron) is necessary to ensure the benefits outweigh its risks. Urovant Sciences (Urovant) submitted a New Drug Application (NDA) 213006 for vibegron with the proposed indication of treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. The risk associated with vibegron is urinary retention. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM along with the Division of Urological, Obstetrics and Gynecological Products (DUOG) agree that a REMS is not needed to ensure the benefits of vibegron outweigh its risks. The most common adverse events for vibegron were hypertension, urinary tract infections, and headache. These adverse events were comparable to the placebo group and or less than the adverse event rates observed with subjects in the tolterodine group. No difference was observed for hypertension events between vibegron and placebo groups, even in those subjects with or without pre-existing hypertension. This differed from Myrbetriq (mirabegron) which is in the same drug class as vibegron, approved in 2012 for OAB, and has a Warnings and Precaution for changes in BP effects. No clinically relevant changes from baseline in postvoid residual (PVR) volume for subjects treated with vibegron compared with placebo were found in the clinical development program for this application. However, due to increase postmarketing reports from Japan for vibegron, marketed as Boeva, the Applicant proposes to include urinary retention risk in the Warnings and Precaution section of the product labeling which is similar to Myrbetriq's labeling.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Gemtesa (vibegron) is necessary to ensure the benefits outweigh its risks. Urovant submitted a New Drug Application (NDA) 213006 for vibegron with the proposed indication of treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. This application is under review in the Division of Urology, Obstetrics, and Gynecology (DUOG). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Vibegron, a new molecular entity[a], is a selective agonist of the human beta-3 adrenergic receptor (β3-AR) proposed for the use in the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency. The primary mechanism of action is through bladder relaxation during the filling phase and inhibition of the frequency of non-voiding activity, thus enhancing urine storage.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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Vibegron is supplied as an oral tablet and is intended to be used daily. The proposed dosing regimen is one 75 mg tablet daily with or without food. Vibegron will most likely be administered in an outpatient or long-term care setting. The duration of treatment for OAB is long-term.[b] Vibegron is not part of a drug class that has a boxed warning or REMS. Vibegron is currently approved and marketed in Japan as Boeva at 50 mg daily.[c]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213006 relevant to this review:

- 12/26/2019: NDA 213006 submission for treatment of treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency received
- 06/15/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for vibegron.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Overactive bladder (OAB) is a clinical syndrome characterized by urinary urgency with or without urinary incontinence, often accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathology.[1] OAB is estimated to affect greater than 400 million people worldwide with rates ranging from 7-27% in men and 9-43% in women.[2d] Multiple studies demonstrated that living with OAB has negative effects on numerous quality of life domains including recreational life, depression, isolation, sexuality, and work productivity.[1e]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

First line treatments for OAB include modifying contributory medical and lifestyle factors and initiating pelvic floor exercises and bladder training. In the United States (US), two classes of medications are available for pharmacologic treatment: antimuscarinic agents and beta-adrenergic agonists. Anti-muscarinic agents including darifenacin, fesoterodine, oxybutynin, solifenacin, and tolteradine act by increasing bladder capacity and decreasing urgency through blockage of muscarinic receptor stimulation by acetylcholine during bladder storage. These agents may cause dry mouth, constipation, blurred vision, tachycardia, drowsiness, and decreased cognitive function. Mirabegron, a beta-adrenergic agonist, acts by bladder relaxation during the filling phase and inhibition of the frequency of non-voiding activity, thus enhancing urine storage. Mirabegron is associated with potential treatment associated

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[c] International birthdate September 21, 2018.
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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hypertension. None of the currently approved pharmacotherapies approved for OAB has a risk evaluation and mitigation strategy (REMS). The Applicant states that vibegron, a beta-3 agonist, similar to mirabegron, would broaden the treatment landscape and offer an alternative treatment option for patients with OAB. The following table summarizes currently available products approved in the US for OAB.

Table 1: Summary of Pharmaceutical Treatment Options for OAB

Established Name (Trade Name)	Year of Approval	Dosing/Administration	Important Safety Issues in Labeling (Warnings and Precautions)
Anti-muscarinic Agents			
Darifenacin (Enablex)	2004	7.5 mg once daily	• Risk of urinary retention • Decreased gastrointestinal mobility • Use caution in patients with narrow-angle glaucoma • Angioedema
Fesoterodine (Toviaz)	2008	4 mg once daily	
Oxybutynin (Ditropan)	1975	5-10 mg once daily	
Solifenacin (Vesicare)	2004	5 mg once daily	
Tolterodine (Detrol LA)	2000	2-4 mg once daily	
Beta-3 Adrenergic Agonists			
Mirabegron (Mybetriq)	2012	25 mg once daily	• Increases in blood Pressure • Urinary Retention • Angioedema

4 Benefit Assessment

The efficacy and safety of vibegron 75 mg once daily for the treatment of OAB was demonstrated in the pivotal phase 3 randomized, double-blind, placebo and active controlled multi-centered study (Study 3003 [NCT03492281]) and its associated long-term (52 weeks) efficacy and safety extension study (Study 3004 (NCT03583372).[3,4] The Applicant also submitted a phase 1 ambulatory blood pressure monitoring (ABPM) study (Study 1001) in support of cardiovascular safety of vibegron for changes in blood pressure (BP) as mirabegron has this risk listed in its labeling.

The primary endpoint of Study 3003 was the change from baseline at week 12 in the average number of micturition per 24 hours in all OAB subjects and change from baseline at week 12 in the average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB wet subjects. Secondary endpoints include change from baseline in urgency episodes, total incontinence episodes, Overactive Bladder Questionnaire Long-Form (OAB-q LF), and volume voided per micturition.

Study 3003 randomized 1515 patients (5:5:4) to receive, vibegron 75 mg (n=545), placebo (n=540) or tolterodine ER 4 mg (n= 430) daily over a 12-week treatment period. The change from baseline in

average daily number of micturition at week 12 was significantly greater in the vibegron group vs placebo (-1.8 vs -1.3, least square (LS) means difference of -0.5, p<0.001). The change from baseline the number of average daily number of UUI was also significantly greater in the vibegron group vs placebo (-2 vs -1.4, LS means difference of -0.6, p<0.0001). Therefore, for the primary endpoint analysis, the results are highly statistically significant for the co-primary endpoints of the vibegron treatment arm compared to placebo. Vibegron treatment was also statistically significantly more effective than placebo for the secondary endpoints of average daily number of urgency episodes (LS means difference of -0.7 (p = 0.002), total incontinence episodes (LS means difference -0.7 (p < 0.0001), OAB-q LF Coping score [f](LS means difference (b) (4)), and average volume voided per micturition (LS means difference 21.3 (p < 0.0001). The results of Study 3004 showed durable effects of vibegron treatment over 52 weeks for similar primary and secondary endpoints seen in Study 3003 for primary and secondary endpoints. Some of the key findings from Study 3004 include the primary endpoints of micturition (LS means difference [standard error] for change from baseline (CFB) at Week 52: -2.4 [0.24], 95% CI: -2.9, -2.0); UUI episodes (LS means difference [SE] for CFB at Week 52: -2.2 [0.15], 95% CI: -2.5, -1.9); and for key secondary endpoint such as number of urgency episodes (LS means difference [SE] for CFB at Week 52: -3.4 [0.34], 95% CI: -4.0, -2.7).

As the efficacy results are derived from patient reported outcome (PRO), DUOG consulted the Clinical Outcome Assessment (COA) team for their input on adequacy of the clinical outcome assessment instruments used in Patient Voiding Diary (PVD) endpoints including urinary frequency (micturition), UUI, and Urgency episodes or "need to urinate immediately" (exact language in the PVD), and OAB-q LF Coping Domain (b) (4) The COA reviewer concluded that the Applicant provided content validity for PVD and appears fit-for-purpose in the context of this particular drug development program to measure urinary frequency, UUI episodes, and urgency episodes. However, the Applicant did not provide adequate documentation of content validity to support the OAB-q LF Coping domain (b) (4)

(b) (4)

5 Risk Assessment & Safe-Use Conditions

Support for the safety of vibegron primarily focuses on the results from Study 3004 which included 506 subjects exposed to either vibegron 75 mg (n=274) or tolterodine ER 4 mg (n= 232) in a double-blind, 40-week extension study (up to total of 52 weeks of treatment) for subjects who completed Study 3003. Subjects who were randomized to vibegron or tolterodine ER continued the same blinded treatment, while subjects who were randomized to placebo were re-randomized to vibegron or tolterodine. In

[f] A change from baseline of > 10 points is considered to support the clinical significance of perceived treatment benefit for vibegron efficacy. A higher proportion of vibegron-treated subjects (61.9%) compared with the placebo group (54.4%) achieved this meaningful difference of the QAB-qLF Coping Score.
[g] Chang, D. Wrap-up meeting for vibegron, NDA 213006, dated October 28, 2020.

addition, the Applicant submitted an ABPM study (Study 1001) to inform on the safety of vibegron on blood pressure.

5.1 ADVERSE EVENTS (AEs)

Vibegron was generally well tolerated among subjects receiving vibegron for up to 52 weeks in Studies 3003 (12 weeks) and 3004 (40 weeks) combined. No clinically meaningful differences were observed for the vibegron group compared with the tolterodine group in the overall incidence or severity of AEs, the incidence of severe adverse events (SAEs), or the incidence of AEs leading to study drug discontinuation. The most commonly occurring adverse reactions associated with vibegron include hypertension (8.8%), urinary tract infections (6.6%), and headache (5.5%). See Table 2 below for tabulation of common AEs.

Table 2: Adverse Events Reported in > 2 % of Subjects Receiving Vibegron 75 mg (Study 304)

Preferred Term	Vibegron 75 mg N = 273 n (%)	Tolterodine ER 4 mg N = 232 n (%)
Any AE	**171 (62.6)**	**126 (54.3)**
Hypertension	24 (8.8)	20 (8.6)
Urinary tract infection	18 (6.6)	17 (7.3)
Headache	15 (5.5)	9 (3.9)
Nasopharyngitis	13 (4.8)	12 (5.2)
Diarrhoea	13 (4.8)	4 (1.7)
Upper respiratory tract infection	10 (3.7)	1 (0.4)
Constipation	10 (3.7)	6 (2.6)
Nausea	10 (3.7)	7 (3.0)
Bronchitis	8 (2.9)	3 (1.3)
Anaemia	7 (2.6)	2 (0.9)
Residual urine volume increased	7 (2.6)	3 (1.3)
Hyperglycemia	7 (2.6)	2 (0.9)
Back pain	6 (2.2)	3 (1.3)
Musculoskeletal pain	6 (2.2)	1 (0.4)

Source: Study 3004 CSR Table 14.3.1.13
AE = adverse event; ER = extended release; SAF–Ext = Safety Set Extension
Notes: Includes cumulative data from Study 3003 for subjects who received vibegron or tolterodine in Study 3003
Overall Vibegron 75 mg includes patients who received 52-weeks and 40-weeks Vibegron 75 mg and Overall Tolterodine ER 4 mg includes patients who received 52-weeks and 40-weeks Tolterodine ER 4 mg. Only data for patients on active treatment were included.
Descriptions of AEs are coded using Medical Dictionary for Regulatory Activities version 20.1.
Presented frequencies and the denominator used for percentages are based on patients in the SAF-Ext and the actual treatment received.
Patients with multiple AEs within the same System Organ Class and/or Preferred Term are only counted once within the respective category.

5.2 DEATHS

Three deaths occurred during the clinical development program for vibegron. None of the deaths were attributed to vibegron.

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- A 75 year old female receiving tolterodine in Study 3003 died due to cerebrovascular incident 62 days after initiating the study.
- A 63 year old female receiving 75 mg vibegron in Study 3004 died 102 days after initiating study drug due to arteriosclerotic lesion. No autopsy was performed, and the death was deemed unrelated to the study drug.
- A 69 year old female receiving 50 mg vibegron in a Phase 2 study, died 29 days after initiating study drug. The death was attributed to a cervical spinal cord injury resulting from a fall. The patient had been drinking alcohol on the day of the death and the fall was considered accidental and unrelated to the study drug.

5.3 HYPERTENSION

As mirabegron has a risk for increases in blood pressure (BP), DUOG consulted the Interdisciplinary Review Team for Cardiac Safety (IRT-CS) to evaluate the effects of vibegron on AMBP from Study 1001.[6,7]

Study 1001 is a randomized, placebo-controlled, phase 1 ABPM study with 197 OAB patients receiving vibegron 75 mg once daily (n = 96) or placebo (n = 101) for 28 days. The primary endpoint was change from baseline compared to placebo for daytime systolic BP (daytime: 8a to 10p and night time: 10p to 8a). The daytime period was determined via diary. Secondary endpoints include changes in diastolic BP and HR. A two-sided confidence interval (CI) with alpha of 0.05 was used in the analysis to detect a mean 24-hour ambulatory systolic BP < 3 mmHg.

The IRT-CS reviewer concluded that vibegron showed no significant increases in placebo-adjusted mean changes from baseline in daytime and 24-hour average systolic BP (0.5, [95% CI: -1.3 to 2.4]), diastolic BP (-0.3, [CI: -1.5 to 1]) and heart rate (HR) (1, [CI: -0.3 to 2.2]). Further analysis conducted by the IRT-CS reviewer using the Pool Cohort Equationsh to predict 10-year risk for atherosclerotic cardiovascular disease (ASCVD) events estimated an ASCVD event rate of ≤0.2 ASCVD per 1000 patient years using the upper-bound of the change from baseline in the 24-h average SBP for vibegron 75 mg once daily. Based on the ABPM study results, the IRT-CS reviewer concluded that vibegron is not associated with a clinically significant increased risk of hypertension and the clinical reviewer concurred with this finding.

5.4 URINARY RETENTION

Study 3003 reported urinary retention in 2 subjects (0.4%) receiving placebo and 3 subjects (0.6%) receiving vibegron. In addition, 3 subjects (1.1%) receiving vibegron in Study 3004 had urinary retention. There was no clinically relevant change from baseline in postvoid residual volume (PVR) at Week 12 (Study 3003) and up to Week 52 (Study 3004) for subjects treated with vibegron compared with placebo. In study 3003, the mean (SD) changes from baseline at Week 12 were: placebo 2.1 (37.25) mL; vibegron 0.4 (38.27) ml; tolterodine ER 3.1 (40.93) ml. Thus, treatment with vibegron did not result in increased urinary retention in subjects (males and females) with OAB.

[h] Pool Cohort Equation estimates the 10-year primary risk of ASCVD among patients without pre-existing cardiovascular (CV) disease who are between 40 and 70 years of age based on the American College of Cardiology and American Heart Association (ACC/AHA) Guideline on the Assessment of CV Risk. The predicted ASCVD risk can be categorized into low risk (<7.5%), intermediate risk (≥7.5% to <20%) and high risk (≥20%).

However, urinary retention was one of the most frequently reported events in postmarketing experience with Beova, currently marketed by Kyorin in Japan. In the postmarketing setting, 11 serious and 44 nonserious events of urinary retention were reported as of the data cutoff date for this submission (01 August 2019). The Applicant noted that review of the clinical study data and postmarketing data showed that urinary retention was reported in subjects ≥ 60 years old and predominantly in subjects with bladder outlet obstruction. Given spontaneous reports of urinary retention with Beova, the Applicant proposes to add this adverse drug reaction as Warning in the vibegron prescribing information and is consistent with mirabegron labeling. The clinical reviewer concurs with the inclusion of this risk in labeling.

6 Expected Postmarket Use

The likely prescribers for vibegron will be general practitioners, obstetricians, gynecologists and urologists which are the same prescribers for the existing approved treatments for OAB. Vibegron will be prescribed primarily in outpatient and long-term care settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for vibegron beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of vibegron on the basis of the efficacy and safety information currently available.

Symptoms of OAB are urinary frequency, urinary urgency, and urge urinary incontinence. OAB is estimated to affect greater than 400 million people worldwide impacting negatively on the quality of life as patients are often prevented from fully engaging in activities of daily life and may also result in the incumbrance of hygiene issues or embarrassment.

The pivotal trial (Study 3003) showed that vibegron achieved the primary endpoints. The change from baseline in the average daily number of micturition at week 12 was significantly greater in the vibegron group vs placebo and the change from baseline in the average daily number of UUI was also significantly greater in the vibegron group vs placebo in patients with OAB. Secondary endpoints of average daily number of urgency episodes, total incontinence episodes, OAB-q LF Coping score, and average volume voided per micturition were also of statistical significance, however, the COA and clinical reviewers concluded that the validity of OAB-q LF results may be inadequate (b) (4) Study 3004, the associated long-term (total 52 weeks) extension study of 3003 showed durable vibegron effects.

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The adverse event profile of vibegron is similar to other β3-AR treatments for OAB. Consistent with β3-AR class for OAB, the safety concern for urinary retention will be included in the Warning and Precautions section of the Prescribing Information. Unlike mirabegron, there were no clinically significant changes to ABPM effects with vibegron and its prescribing information will reflect this difference.

Therefore, based on the available data and the prescribing community's likely familiarity with the risks associated with vibegron which do not pose unique REMS considerations compared with the risks associated with other OAB therapies, a REMS is not necessary to ensure the benefits of vibegron outweigh the risks. Labeling will adequately communicate the risk of urinary retention.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risk. Vibegron was effective in reducing the number of urgency episodes and total incontinence episodes, and increasing the volume voided per micturition. Additionally, the safety concerns for urinary retention associated with vibegron use are well documented for this drug class. The adverse event profile is similar to the other beta-3 adrenergic agonist such as urinary tract infections and headache. Therefore, based on available data, the safety and risk mitigation approach of this drug compared to other drugs in the class, the risks can be adequately communicated via labeling.

Should DUOG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 References

1. Corcos J, Przydacz M, Campeau L, et al. CUA guideline on adult overactive bladder. *Can Urol Assoc J.* 2017;11(5):E142-e173.
2. Rosa GM, Ferrero S, Nitti VW, Wagg A, Saleem T, Chapple CR. Cardiovascular Safety of β3-adrenoceptor Agonists for the Treatment of Patients with Overactive Bladder Syndrome. *Eur Urol.* 2016;69(2):311-323.
3. Urovant Sciences. NDA 213006. Summary of Clinical Efficacy, dated December 26, 2019.
4. Urovant Sciences. NDA 213006. Summary of Clinical Safety, dated December 26, 2019.
5. Ghafoori P. Clinical Outcome Assessment Consult Review for Gemtesa (vibegron) NDA 213006, dated October 14, 2020.
6. Lars J. IRT-CS Review for ABPM Study for NDA 213006, dated May 7, 2020.
7. Hsu Y. IRT-QT Review for NDA 213006, dated June 19, 2020.

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