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APPLICATION NUMBER:

213006Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Update Review

Date	December 18, 2020
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Update Memo
NDA/BLA# /Supplement#	213006
Applicant	Urovant
Date of Submission	December 25, 2019
PDUFA Goal Date	December 26, 2020
Proprietary Name / Established (USAN) names	GEMTESA vibegron
Dosage forms / Strengths	75 mg oral tablet taken once daily
Indication(s)	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency
Recommended:	<i>Approval</i>

The purpose of this CDTL Update review is:

- 1) To confirm my CDTL agreement with the review team's recommendation for Approval of this application,
- 2) To provide brief summaries of the discipline-specific and consultative FDA reviews for this application, and;
- 3) To address the status of (and confirm my agreement with) the labeling for this application.

1. Confirm CDTL Agreement with Recommendation for Approval

CDTL Note: For detailed information on the regulatory history and benefits/risks of GEMTESA (vibegron) for the treatment of OAB, the reader is referred to the December 9, 2020, Clinical Review, with special attention to the following sections:

- 1) *Summary of Presubmission/Submission Regulatory Activity*
- 2) *Integrated Review of Effectiveness (Section 7), and*
- 3) *Integrated Assessment of Safety (Section 8.10).*

Herein, I provide an overview of the product, the indication, and the Efficacy and Safety conclusions based on the reviews from the Clinical and Statistical teams. I also confirm my agreement with the NDA review team that GEMTESA should be approved for the treatment of OAB because the benefits of GEMTESA outweigh the risks.

In brief, vibegron is an agonist of the human beta-3 adrenergic receptor (β_3 -AR), developed for the treatment of OAB. Beta-3 adrenergic receptors are found in the bladder base and walls.

Stimulation of β 3-AR in those locations results in relaxation of the bladder detrusor muscle with resultant increase in urine storage capacity and reduced spontaneous detrusor muscular contractions.

OAB, including symptoms of urinary urgency, frequency and urge urinary incontinence, is a prevalent chronic condition in the US, with increased prevalence in the geriatric population. OAB is known to adversely affect a patient's quality of life, especially those patients with incontinence. Current treatment methods for OAB include: 1) nonpharmacologic (first-line) methods, such as weight loss, pelvic floor training and biofeedback, 2) oral pharmacologic therapy, including a) muscarinic antagonist medications for OAB, such as tolterodine, oxybutynin, solifenacin, darifenacin, etc., b) the β 3-AR mirabegron, and c) a combination of solifenacin and mirabegron, 3) invasive local pharmacologic therapy with intra-detrusor injections of botulinum toxin, and finally, 4) procedural and surgical therapies, including peripheral nerve stimulation and sacral nerve neuromodulation with an implanted electrical stimulator.

GEMTESA, the second β 3-AR for treatment of OAB, will add to the pharmacologic armamentarium for OAB. Notably, GEMTESA has no clinically meaningful effect on blood pressure, which may improve its clinical utility for the treatment of OAB, especially in geriatric patients.

The efficacy of GEMTESA has been demonstrated in three (3) randomized, double-blind, placebo- and active-control studies, as follows:

- Study RVT-901-3003 (Study 3003): a Phase 3, U.S., randomized, double-blind, placebo- and active-controlled, 12-week, pivotal efficacy and safety study (dose of vibegron studied: 75 mg daily)
- Merck Study 008: a Phase 2b, randomized, double-blind, placebo- and active-controlled, 8-week, dose-ranging, supportive efficacy and safety study (doses of vibegron studied: 3mg, 15 mg, 50mg and 100mg daily)
- Study KRP114V-T301 (Kyorin 301): a Phase 3, Japanese, randomized, double-blind, placebo- and active-controlled, supportive efficacy and safety study (doses of vibegron studied: 50 mg and 100mg daily)

In these three (3) placebo-controlled studies, vibegron demonstrated consistent effectiveness versus placebo for the treatment of OAB based on improvements in the standard co-primary endpoints for OAB studies: reduced number of daily micturitions compared to placebo in the overall OAB population, and reduced number of urge urinary incontinence episodes (UUI) compared to placebo in the subpopulation with incontinence (“Wet OAB”).

Vibegron-related improvements over placebo were also demonstrated for a host of secondary efficacy endpoints, including 1) increased average volume voided per micturition, 2) reduced number of episodes of “need to urinate immediately” (urgency), 3) reduced number of micturitions and UUI episodes at certain timepoints: e.g., Weeks 2 and 12 (in Studies 3003 and

Kyorin 301) and Week 52 (in Study 3004, the double-blind, active-controlled, extension to Study 3003, and in the Merck Study 008 extension phase), 4) vibegron-related increases in treatment “responders” based on pre-specified responder thresholds (e.g., 50%, 75%, and 100% reduction in events), and 5) vibegron-related improvements in patient-reported outcome (PRO) measures, including the OAB-Questionnaire Long-Form (OAB-q LF) and patient global assessment instruments.

Efficacy was also evaluated in Study RVT-901-3004 (Study 3004), a Phase 3, U.S., randomized, double-blind, active-controlled (only), 40-week, safety and efficacy, supportive extension study of Study 3003 (dose of vibegron studied: 75 mg daily). In this active-controlled study, efficacy was assessed as a secondary objective. Nevertheless, the efficacy results for vibegron from this long-term study were consistent with the results for vibegron from the three (3), randomized, placebo-controlled studies and were comparable to the results for the concurrent active control.

From an effectiveness standpoint, the Clinical review focused on Urovant U.S. Study 3003 because it was the only study to investigate a dose of 75 mg once daily, the to-be-marketed dose regimen. The reader is referred to the Clinical review for details on the specific vibegron-related efficacy data from Study 3003. In brief, Study 3003 confirmed the pre-specified treatment effects of vibegron 75 mg daily on the standard co-primary and secondary efficacy endpoints, and in addition, a vibegron-related beneficial effect was demonstrated on the novel “need to urinate immediately” (urgency) endpoint. Urgency is a critical component of the OAB syndrome and for many OAB patients, it is their most bothersome symptom.

CDTL Note: In my opinion, the reliable, positive effect of GEMTESA on urgency, the key symptom of OAB, is also an important part of this approval and represents good news for health care practitioners and OAB patients.

Finally, it should be noted that the efficacy results for vibegron are comparable to efficacy results shown for mirabegron (Myrbetriq), a β_3 -AR that was discussed at an April 5, 2012 meeting of the Bone, Reproductive and Urologic Advisory Committee (BRUDAC). At the meeting, the BRUDAC determined that the efficacy results for mirabegron - which are comparable to the efficacy results for vibegron - supported the effectiveness of mirabegron for the treatment of OAB.

Taken together, the efficacy evidence from the adequate and well-controlled pivotal Study 3003 and the confirmatory placebo-controlled studies (Merck Study 008, and Kyorin Study 301) support the effectiveness of GEMTESA for the treatment of OAB. The data also support a secondary claim for urgency (“need to urinate immediately”) when part of OAB symptomatology.

The safety of GEMTESA was evaluated in total of 3190 subjects who received at least one dose of vibegron, including 566 healthy volunteers in 20 Phase 1 studies and 2625 OAB subject who received vibegron in 5 Phase 2b and Phase 3 clinical studies. Overall, 513 and 305 patients received vibegron 75 mg or 100mg daily for at least 6 months and 1 year,

respectively. Of note, ambulatory blood pressure monitoring (ABPM) and through QT (TQT) studies were conducted for vibegron.

The safety profile of GEMTESA in patients with OAB was shown to be consistent or better than the known safety profile of mirabegron, the only currently approved β 3-AR for the treatment of OAB. The adverse reactions for GEMTESA in the 12-week studies (Study 3003 and Kyorin 301) included headache, nasopharyngitis, diarrhea, nausea, and upper respiratory infection, all reported at low frequencies, all just modestly greater than placebo. In the long-term studies of up to 52-week duration (Urovant Study 3004, Kyorin 302, and Merck Study 008 extension), the safety profile of GEMTESA was consistent with its safety profile in the 12-week studies, with the same adverse reactions reported just at higher frequencies, a result consistent with longer treatment durations. Two additional adverse reactions reported in long-term studies were urinary tract infection and bronchitis. In the postmarketing period in Japan, spontaneous adverse event reports received to date have been consistent with the GEMTESA safety profile from clinical trials, with two notable types of events: urinary retention, especially in men with co-morbid benign prostatic hyperplasia and skin allergic-type reactions, including generally non-serious rash, pruritis, drug eruption and eczema.

Finally, it is worth noting that the ABPM study and TQT studies were both negative, with no clinically meaningful effects for vibegron on BP or the corrected QT interval.

Thus, efficacy and safety data from the adequately controlled trial (Study 3003) along with the supportive placebo-controlled studies (Merck Study 008, and Kyorin Study 301) that used accepted endpoints for OAB studies have demonstrated that GEMTESA tablets are effective in the treatment of OAB at the 75 mg daily dose. The results from these three trials were consistently statistically significant, and efficacy has been demonstrated in the broad population of patients with OAB and the subpopulation with “Wet OAB”. In addition, the safety profile from the clinical trial database and postmarketing period in Japan is clinically similar to the other currently approved β 3-AR (mirabegron). I confirm my agreement with the review team that this application for GEMTESA for the treatment of OAB should be Approved.

2. Brief Summaries of the Discipline-Specific and Consultative FDA Reviews

CDTL Note: For details on the discipline-specific and consultative reviews completed for this NDA through December 9, 2020, the reader is referred to the final Clinical Review, under “Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.” The reader is also referred to the discipline-specific reviews themselves. Herein, I briefly summarize the completed discipline-specific and consultative reviews.

2.1 Chemistry

In their final Office of Pharmaceutical Quality (**Chemistry**) Integrated Quality Assessment (IQA) dated December 14, 2020, Mark Seggel and Wendy Wilson had the following Conclusion on Approvability:

“As amended, Urovant Sciences’ 505(b)(1) New Drug Application 213006 for GEMTESA (vibegron) tablets, 75 mg, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product.

The labeling and labels as submitted on November 24, 2020 and November 13, 2020, respectively, are accurate, complete and comply with the requirements under 21 CFR 201.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on June 3, 2020. The recommendation remains current as of this review [December 8, 2020].”

Of note, the originally proposed to-be-marketed (TBM) tablets had a (b) (4) film-coat (b) (4)

The Sponsor was advised that the labeling would need to be revised (b) (4). Once aware of this requirement, the Sponsor re-considered (b) (4). After discussions with the Division about reverting to the light-green, film-coat used in the Phase 3 clinical trial material, the Sponsor decided to replace the (b) (4) film-coat with the light-green, film-coat. The new TBM tablets differed from the clinical trial material (b) (4)

At FDA’s request, to support this change in film-coat, The Sponsor provided comparative dissolution data, as well as 1- and 3-months accelerated stability data and 3-months long-term data from one batch. The dissolution data showed that both formulations had similar release profiles and complied with dissolution acceptance criteria. The additional stability data were consistent with the data from the primary and supporting stability batches.

CDTL Note: No outstanding CMC issues remain and no postmarketing commitments were recommended.

2.2 Pharmacology/Toxicology

In their final **Pharmacology/Toxicology** review dated October 20, 2020, Laurie McLeod-Flynn and Kim Hatfield had the following Conclusion:

“Pharmacology/toxicology supports approval of vibegron 75 mg for the treatment

of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.”

Of note, accumulation of brown fat was observed in male rats in a 6-month toxicity study, and slight accumulation of brown fat was observed in white adipose tissue in Rhesus monkeys in a 9-month toxicity study. The Pharmacology/toxicology team characterized these findings as “...*pharmacological effects common to beta-3-adrenergic agonists in animals*”.

CDTL Note: No outstanding Pharmacology/toxicology issues remain and no postmarketing requirements or commitments were recommended.

2.3 Clinical Pharmacology

In their final **Clinical Pharmacology** review dated October 23, 2020, Lin Zhou and Yanhui Lu had the following Conclusion:

“The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology, has reviewed the information contained in NDA 213006 and recommends approval of this NDA”.

A key point from the Clinical Pharmacology review was the drug-drug interaction (DDI) potential with digoxin. Concomitant administration of vibegron increased digoxin C_{max} and AUC by 21% and 11%, respectively. Because digoxin is a narrow therapeutic index drug, the observed increase in digoxin was considered clinically relevant and specific recommendations were instituted in labeling for digoxin monitoring in patients taking vibegron.

CDTL Note: The digoxin interaction study was conducted at a dose of 100 mg early in drug development when the 100 mg dose was still being considered for Phase 3 studies. Following the dose-ranging Merck Study 008, the Sponsor determined that a 75 mg daily dose provided the best possible benefit/risk profile. No outstanding Clinical Pharmacology Issues remain and no postmarketing requirements or commitments were recommended.

2.4 Biometrics

In their final **Statistical** review dated October 28, 2020, Jia Guo and Daphne Lin had the following Conclusion:

“...Based on reviewer’s analyses, the results supported the efficacy of vibegron 75 mg in the improvement of the protocol specified co-primary endpoints and the selected secondary efficacy endpoints. From a statistical perspective, vibegron 75mg was effective in treating OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.”

CDTL Note: No outstanding Statistical issues remain.

2.5 Clinical

In our final **Clinical** review dated December 9, 2020, Debuene Chang and I had the following Recommendation:

“Vibegron, a new molecular entity, is a selective agonist of the human beta-3 adrenergic receptor (β_3 -AR), developed for treatment of overactive bladder (OAB) with 75 mg oral daily dosage. Recommendation: Approval”

In regard to efficacy and safety, the Clinical review stated:

- *“The Sponsor has submitted evidence of effectiveness that meets the statutory evidentiary standard.”*
- *“The safety profile is well-characterized and shows relative balance between vibegron and placebo”.*

CDTL Note: I agree with the Clinical reviewer that no outstanding clinical issues were identified that require postmarketing requirements or commitments.

2.6 Office of Scientific Investigation (OSI)

In their final **Clinical Inspection Summary** dated October 9, 2020, Ling Yang, Min Lu and Kassa Ayalew stated:

“Based on the results of these CI inspections, Study RVT-901-3003 and RVT-901-3004 appear to have been conducted adequately, and the data generated by these sites and submitted by the Sponsor appear acceptable in support of the respective indication”.

2.7 Division of Cardiology and Nephrology (DCN)

2.7.1 Interdisciplinary Review Team for Cardiac Studies - QT Study Review

In their final **IRT-QT** review dated June 19, 2020, Yu Yi Hsu, Dalong Huang, Raman Baweja, Nan Zheng, Michale Li, Lars Johannesen, and Christine Garnet had the following Conclusion:

“No significant QTc prolongation effect of vibegron was detected in this QT assessment”.

2.7.2 Interdisciplinary Review Team for Cardiac Studies – ABPM Study Review

In their final **IRT-QT** review dated June 19, 2020, Lars Johannesen, Fortunato Senatore, Christine Garnet and Norman Stockbridge team had the following Conclusion:

“No significant effects of vibegron on blood pressure (BP) was observed in this ABPM study as evidenced by an upper bound of 1.7 mmHg for the mean change from baseline in systolic BP”.

In their August 27, 2020, response to a follow-up question concerning any potential effect on BP in lower weight subjects, Lars Johannesen, Christine Garnett and Norman Stockbridge stated:

“The submitted data do not support drug effects on BP and HR in the lower weight groups.”

In their September 22, 2020, response to follow-up questions concerning the results of pharmacodynamic interaction studies with tolterodine, metoprolol and amlodipine, Christine Garnett, Preston Dunmon and Norman Stockbridge stated:

For tolterodine: *“There is no clinically meaningful increase in HR...lack of a HR effect was also observed in the ABPM study”*.

For metoprolol and amlodipine: *“Vibegron 75 mg QD does not increase or decrease BP as demonstrated in the ABPM study and there were no large decreases in BP when vibegron 100 mg QD was coadministered with metoprolol or amlodipine.”*

2.8 Division of Clinical Outcomes Assessment (DCOA)

In their final **DCOA** review dated October 14, 2020, Parima Ghafoori, Selena Daniels and Elektra Papadopoulos had the following Conclusions:

- *“The PVD (patient voiding diary) appears fit-for-purpose in the context of this particular drug development program to measure urinary frequency, UUI episodes, and urgency episodes”*.
- *“The PVD appears adequate to support labeling claims. Regarding labeling the concept of urgency, we recommend using the exact language of the concept measured [i.e., “urgency (need to urinate immediately)”] in the PVD”*.
- *(For the PVD-related endpoints), “...there is uncertainty about the threshold that best represents a meaningful within-patient score change as the results from the phase 3 study (Study 3003) show a considerably higher threshold compared with the results obtained from the phase 2 study (Study 008).”*
- *“The submission did not include adequate documentation of content validity to support the OAB-q LF Coping domain [REDACTED] (b) (4) ...”*

2.9 Office of Prescription Drug Promotion (OPDP)

In their final **OPDP** review dated November 18, 2020, Elvy Varghese and Matthew Falter stated:

“OPDP’s comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Nenita Crisostomo) on November 10, 2020 and are provided below...”

All labeling comments from OPDP were addressed, either through internal discussion or by instituting labeling changes.

2.10 Division of Medical Policy Program (DMPP)

In their final *Patient Labeling* review dated November 20, 2020, Lonice Carter, Elvy Varghese, Sharon Williams and LaShawn Griffiths had the following Conclusion:

“...The PPI is acceptable with our recommended changes.”

All labeling changes recommended by DMPP were instituted.

2.11 Division of Medication Errors Prevention and Analysis (DMEPA)

In their final *DMEPA* labeling reviews dated July 9, 2020 and June 1, 2020, Denise Baugh and Briana Rider had the following Conclusions:

For carton and container labeling

“The Applicant implemented or considered all of our recommendations and we have no additional recommendations at this time”.

For the Prescribing Information labeling

“...we reviewed the proposed Prescribing Information (PI) and Patient Information labeling. We note the statement (b) (4) appears in Section (b) (4) of the PI and in the Patient Information. We are concerned that this statement may be misinterpreted (b) (4)

(b) (4) We communicated our concerns to OPQ, and they clarified (b) (4) We provide recommendations....to address these concerns”.

All labeling edits recommended by DMEPA were instituted.

In their final tradename review dated March 6, 2020, Justine Kalonia and Briana Rider had the following Conclusion:

“The proposed proprietary name, Gemtesa, is acceptable”.

2.12 Division of Risk Management (DRM)

In their final review dated December 9, 2020, (DRM) had the following conclusion:

“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.”

2.13 Pediatric Review Committee (PeRC)

The final meeting minutes from the November 5, 2020, *PeRC* meeting stated:

“The PeRC agrees with the request for waiver in pediatrics less than 3 years of age

and deferred studies in pediatrics 3 to less than 17 years of age. The PeRC recommends the Sponsor advance the dates for the PMRs by one year.”

The recommendation of the PeRC was instituted.

CDTL Note: The Applicant will be required to conduct a postmarketing requirement (PMR) in pediatric patients with neurogenic detrusor overactivity (NDO) and requested a deferment for patients 3 to 17 years of age and a partial waiver for patients under 3 years of age with NDO (because studies are highly impractical in this age group) under the Pediatric Research Equity Act (PREA) requirement. The timelines has been discussed with PeRC and agreed to by the Applicant and will be included in the Approval letter. The protocol for this pediatric study will be reviewed during the post-approval period.

3. Confirm CDTL Agreement with Labeling

Labeling discussions were held with the entire FDA review team on September 21, 2020, October 7, 2020, October 14, 2020, October 28, 2020, November 3, 2020 and November 6, 2020.

The Division’s edits to the PI were conveyed to the Sponsor on November 10, 2020. The Sponsor accepted most of the Division’s proposed edits and returned the PI with several revisions on November 24, 2020.

Labeling discussions with the entire FDA team resumed on December 7, 2020. The Division accepted some of the Sponsor’s revisions and rejected others. Of note, (b) (4) following internal discussions between the Clinical, Statistical, DCOA review teams, and DUOG’s Associate Director of Labeling (ADL). The FDA-edited PI was conveyed to the Sponsor on December 8, 2020.

The Sponsor accepted all the Division’s edits except for two. The first edit pertained to the FDA’s request for a different exact volume of distribution (Vd) for vibegron 75 mg in the Pharmacokinetics section. The Sponsor calculated a different Vd, based on a result from a different study. Clinical Pharmacology asked that the FDA-requested Vd be replaced. The second edit pertained to the Division’s request (b) (4) For several number reasons, the Sponsor requested not to include (b) (4)

In follow-up, the Sponsor accepted the FDA-requested Vd and the Division agreed not to include (b) (4) Final agreed-upon PI was received from the Sponsor on December 17, 2020.

For the PPI, the Division’s edits were conveyed to the Sponsor on December 8, 2020. The Sponsor accepted all of the Division edits and returned the PPI on December 10, 2020. One minor revision was requested by DMPP and that change was instituted.

A final, agreed-upon PPI was received from Sponsor on December 17, 2020.

CDTL Note: I concur with the final agreed-upon PI and PPI. There are no outstanding labeling issues.

Deputy Director Addendum: I concur with the recommendations of the review teams and the CDTL that this Application can be approved. I also concur with the CDTL that substantial evidence of effectiveness has been demonstrated through the placebo-controlled trial (Study 3003) and supportive evidence from Merck Study 008, Kyorin Study 301 and the active-controlled study 3004. The safety profile has sufficient supportive data to meet ICH E10 guidelines and is clinically similar to other approved OAB products, including one that has a similar mechanism of action (mirabegron). Labeling negotiations have concluded and an agreed to label has been reached. In my opinion, the benefit/risk assessment favors approval of GEMTESA (vibegron) for the treatment of overactive bladder.

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/

MARK S HIRSCH
12/18/2020 01:27:34 PM

AUDREY L GASSMAN
12/18/2020 01:39:23 PM