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APPLICATION NUMBER:

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SUMMARY REVIEW

Acting Deputy Division Director Summary Review

Date	June 29, 2012
From	Audrey Gassman, MD
NDA #	202611
Applicant name	Astellas Pharma Global Development, Inc
Date of receipt of original submission	August 29, 2011
PDUFA goal date	June 29, 2012
Proprietary name/established name	Myrbetriq/mirabegron
Dosage Form/strength	Tablet/25 mg and 50mg
Proposed Indication	Treatment of overactive bladder
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Mark Hirsch, MD
Medical Officer Review	Roger Wiederhorn, MD
Statistical Review	Jia Guo, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Eric Andreasen, PhD Lynnda Reid, PhD Abigail Jacobs, PhD
Clinical Pharmacology Review	Sayed Al Habet RPh, PhD Myong-Jin Kim, PhD
ONDQA Review	Bogdan Kurtya, PhD Moo-Jhong Rhee, RPh
ONDQA Biopharmaceutics Review	John Duan, PhD Angelica Dorantes, PhD
Product Quality Microbiology Review	Brian Riley, PhD John Metcalfe, PhD
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CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPP – Division of Professional Promotion
DDTCP – Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Astellas Pharma US, Inc. submitted an NDA (202-611) for a new molecular entity containing a proposed beta-3-adrenergic receptor (β3-AR) agonist in a tablet formulation. The active ingredient is mirabegron (trade name Myrbetriq). Mirabegron is indicated for the treatment of overactive bladder. Although mirabegron is the first of its class, other drug products in the pharmacologic class of muscarinic receptor antagonists, are approved for the "treatment of overactive bladder," in oral, topical and transdermal formulations. Mirabegron has been marked in Japan since July, 2011, for a similar indication at a maximum daily oral dose of 50 mg.

Myrbetriq (mirabegron) is a (b) (4) The primary pharmacology studies show the possible mechanism of action of mirabegron is through bladder relaxation during the filling phase and inhibition of the frequency of non-voiding activity, thus enhancing urine storage.

Mirabegron is supplied as a solid, oval, extended-release (ER) oral tablet and is intended to be used daily. The proposed dosing regimen is one 25 mg tablet once daily. The dose may be increased after 8 weeks to 50 mg based on efficacy and/or tolerability. The Applicant is seeking approval for both the 25 mg and 50 mg tablets. To support approval of this NDA, the Applicant conducted a total of 41 clinical studies that included 29 phase 1 studies and 12 phase 2 /3 studies with over 5,000 subjects exposed to mirabegron in the clinical development program.

The pivotal phase 3 studies formed the basis of the efficacy and safety review. These studies were designed as randomized, double-blind, parallel-group, placebo-controlled multinational studies. The total treatment duration for subjects enrolled in these studies was 12 weeks with efficacy data collected from 3-day micturition diaries during the treatment period. The two co-primary efficacy outcomes for the phase 3 studies included:

- Change from baseline to the final visit (at week 12) in the mean number of incontinence episodes per 24 hours based on a 3 day micturition diary (in subjects with incontinence at baseline)
- Change from baseline to the final visit (at week 12) in the mean number of micturitions per 24 hours based on a 3 day micturition diary

In phase 3 studies, mirabegron demonstrated a statistically significant reduction in incontinence episodes and micturition frequency as compared to placebo at both the 25 mg and 50 mg doses. In addition, benefit was observed for key secondary efficacy endpoints including change from baseline to final visit in mean volume voided per micturition.

Safety issues of concern that were evaluated by review teams during the development program for mirabegron included a potential clinical signal of dose-dependent increases in blood pressure (hypertension) and heart rate (tachycardia). Other safety issues of concern in the mirabegron safety database included: possible delayed hypersensitivity reactions, hepatic adverse events, urinary tract infection events, neoplastic adverse events, and an evaluation of the potential of mirabegron to increase intraocular pressure or induce glaucomatous events.

2. Background

The Applicant initiated discussions on the nonclinical development of mirabegron for the treatment of overactive bladder with the Division of Reproductive and Urologic Products (DRUP) beginning in July, 2004. A pre-IND Type B teleconference was held to discuss safety concerns identified from nonclinical study data.

IND 69416 (mirabegron/YM178 for the treatment of overactive bladder) was officially opened on May, 18, 2006, with a single drug-drug interaction study to assess the pharmacokinetic interaction of multiple dose ketoconazole on single doses of mirabegron.

Since the IND was opened, a total of 41 clinical trials and studies of mirabegron have been conducted that evaluated over 8,000 subjects including doses ranging from 25 mg to 200 mg. The phase 3 program focused on three of the studied doses (25 mg, 50 mg and 100 mg).

An End-of-Phase 2 meeting was held with the Applicant on November 14, 2007. At that time, issues related to CMC, pharm/tox and clinical development were discussed. Key clinical issues raised during that November 2007 meeting included details regarding the co-primary efficacy endpoints and criteria for enrolling men with bladder outflow obstruction. The Division also requested that blood pressure and liver function be carefully monitored in the Phase 3 studies.

On February 5, 2008, following submission of phase 3 study protocols for special protocol assessment (SPA) in December 2007, the Division provided the Applicant with

Phase 3 protocol review comments which recommended that a 25 mg dose of mirabegron be evaluated (b) (4) [redacted]. No agreement on the SPA was reached with the Division. The Applicant initiated the two Phase 3 trials and submitted amended protocols, requesting another SPA on March 5, 2009. In a regulatory letter dated March 16, 2009, the Division informed the Applicant that an SPA cannot be initiated once a study has begun. FDA sent the Applicant comments for the amended protocols on May 20, 2009.

The Division also reviewed other protocols, including those for trials 178-CL-072 and 178-CL-053 (drug-drug interaction) as well as a proposed second thorough QT study (178-CL-077). Other drug development issues were discussed between the Applicant and the Division through preliminary comments and additional meetings held on December 8, 2009 and March 1, 2010 including: 1) metabolite safety testing, 2) the results of thorough QT study 178-CL-037 and the design of QT study 178-CL-077, and 3) the conduct of a long-term safety study 178-CL-075 evaluating the use of mirabegron in males with bladder outlet obstruction at risk for urinary retention and 4) outstanding CMC issues.

At the Pre-NDA meeting held on November 2, 2010, the content and format of the NDA submission were discussed by relevant disciplines including CMC, pharmacology/ toxicology, clinical pharmacology and clinical. As part of the planned NDA, the Sponsor proposed to systematically review adverse events of interest that were identified from the nonclinical and clinical program for mirabegron included:

- Cardiovascular events including hypertension, QT prolongation or its sequelae, cardiac arrhythmias, and cardiac failure;
- Urinary tract events, including urinary retention/acute urinary retention, urinary tract infection, and urolithiasis;
- Hypersensitivity reactions;
- Syncope, postural hypotension and falls;
- Seizures;
- Hepatotoxicity;
- Endocrine/metabolic events;
- Glaucoma; and
- Neoplasms

The Clinical review team concurred with the above proposal to identify and characterize the adverse events of interest in the NDA submission.

NDA 202-611 was submitted to DRUP on August 26, 2011 to support the efficacy and safety of mirabegron. The basis of the NDA clinical review focused on the three phase 3 studies that were conducted in Europe, Australia and North America in subjects with overactive bladder (178-CL-046, 178-CL-047 and 178-CL-074) and also on a long-term controlled study (178-CL-049). Other submitted studies were reviewed as supportive safety studies and included the following: a supportive phase 3 study (178-CL-051), three key phase 2 studies (178-CL-003, 178-CL-008 and 178-CL-060), and 29 phase 1

pharmacokinetic and pharmacodynamic studies including a cardiovascular mechanistic study (178-CL-053), two thorough QT studies (178-CL-037 and 178-CL-077) and an ocular safety study (178-CL-081).

3. ONDQA

Mirabegron (YM178) tablets contain 2-(2-aminothiazol-4-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxy-2- phenylethyl]amino}ethyl)phenyl] acetamide as the active ingredient. The components of mirabegron tablets are commonly used in pharmaceutical products and were controlled by compendial requirements that did not exceed previously approved levels. For polyethylene oxide and the film coating agents (b) (4) the proposed amounts were deemed acceptable by the CMC reviewer. The final tablet formulation was developed to be an extended release formulation in a hydrophilic gel-forming matrix tablet and film-coated (b) (4). All strengths of mirabegron tablets will be packaged in 30 or 90 count HDPE bottles and in an aluminum/aluminum blister package.

The Chemistry Review (ONDQA) team made the following initial recommendation in their review dated April 26, 2012, "The applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product."

The Office of Compliance has issued an overall recommendation of "Acceptable" for the facilities involved in this application (see the Attachment, p. 86). However, an issue on the blister labels is still pending as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21CFR 314.125(b)(6) in its present form until the issue delineated in the "List of Deficiencies" (see p. 85) is satisfactorily resolved."

The basis for the April, 2012, Not-Approval recommendation was that the labels for the blister packs did not have the required information of the name of the manufacturer, packer or distributor.

In an addendum to the April, 2012, ONDQA review, finalized on May 16, 2012, the ONDQA reviewer concluded that resubmitted blister pack labels submitted on May 11, 2012 adequately addressed the Not-Approval recommendation and stated that, "This NDA is now recommended for "Approval" from the ONDQA perspective."

Another memorandum was entered by the ONDQA review team regarding the methods validation consult that was sent on November 1, 2011. The memorandum dated May 22, 2012, stated that, "During the validation process, the FDA laboratory noted that the amount of BHT in the drug product samples was out of specification. However, this is expected result as discussed below, and this observation would not affect our previous "Approval" recommendation."

The ONDQA Biopharmaceutics Review team evaluated the acceptability of the proposed dissolution and acceptance criteria methodology, an in vitro alcohol dose dumping study and an in vivo-in vitro correlation (IVIVC) study. The Biopharmaceutics team concluded on April 24, 2012, that, "NDA 202-611 for Mirabegron ER Tablets is recommended for approval from the Biopharmaceutics perspective."

Comment: There are no outstanding CMC, Biopharmaceutics or Method Validation issues. I concur with the "Approval" recommendation of the ONDQA review team.

4. Nonclinical Pharmacology/Toxicology

Nonclinical data submitted to support approval of mirabegron included assessments of primary pharmacology, safety pharmacology, absorption, distribution, metabolism, elimination, local tolerance, repeat dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity and mechanistic investigations of developmental and cardiac toxicities. The nonclinical review provided a critical assessment and summary of the pharmacology and toxicology. The reviewer stated that, "Findings in animals at exposures similar to the maximum recommended human dose (MRHD) were characteristic of the expected pharmacologic effects for a mixed beta adrenergic agonist including decreased frequency of urination, slight decrease in blood pressure, slight increase in heart rate, and increases in salivation and lacrimation. Toxicities observed in nonclinical studies at exposures greater than at the MRHD include, but are not limited to, hepatotoxicity, effects on body weight and metabolism, impairment of cardiovascular function, and reproductive/developmental effects. These toxicities… were generally at high multiples of the human exposure, and were generally reversible and monitorable."

The elevated heart rates observed in rats, rabbits, dogs and monkeys were at least partially reversed in rabbits, rats, and dogs by metoprolol, suggesting that this is at least partially due to off target beta-1 adrenergic receptor agonism. No adverse drug related ophthalmoscopic findings were reported in any of the species evaluated. Adverse histopathology relevant to humans was not observed except when the drug was administered at large multiples of the maximal clinical exposure. Long-term carcinogenicity assessments in rats and mice and genotoxicity studies were negative.

Mirabegron was transferred to rat fetuses through the placenta and transferred to rat pups in milk. Fertility was not affected in male or female rats below the lethal dose or in offspring exposed in utero and during lactation. Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of adverse developmental effects above background risk. Reversible adverse developmental findings consisting of delayed ossification and wavy ribs in rats and decreased fetal body weights in rabbits occurred at exposures ≥ 22 and 14 times, respectively, the MRHD. At higher maternally toxic exposures decreased fetal weights were observed in rats and rabbits, and fetal death, dilated aorta, and cardiomegaly were reported in rabbits. In utero and lactational exposure at 22 times the MRHD resulted in a slight increase in death of pups during the first four days after birth and a slight decrease in pup weight that was at least partially

recoverable. The Pharmacology/Toxicology group determined that the Pregnancy Category for mirabegron should be a "C".

In conclusion, the pharmacology/toxicology review team stated in their review dated April 12, 2012, that, "The nonclinical data support approval of this product for the treatment of over active bladder in adult patients with symptoms of urge urinary incontinence, urgency, and urinary frequency at a maximum daily dose of 50 mg."

The pharmacology/toxicology supervisor stated in her review (dated April 25, 2012) that there were no outstanding nonclinical issues and concluded, "I concur with the primary nonclinical reviewer, Dr. Eric Andreasen (the primary pharmacology/toxicology reviewer), that nonclinical data support approval of mirabegron at doses up to 50 mg, to be used daily for the treatment of over active bladder in patients with symptoms of urge urinary incontinence, urgency, and urinary frequency." On April 16, 2012, the Associate Director for pharmacology/toxicology also finalized a brief memo stating her concurrence that there were no pharmacology/toxicology approval issues.

Comment: I concur with the approval recommendation of the pharmacology/toxicology review team from a pharmacology/toxicology perspective. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology

The Clinical Pharmacology review team evaluated data from clinical studies that contained relevant Clinical Pharmacology data and presented their findings in a review dated May 22, 2012. The proposed dosing regimen for mirabegron is one 25 mg tablet once daily for 8 weeks prior to titrating up to 50 mg once daily based on efficacy and/or tolerability. For patients with severe renal or moderate hepatic impairment, a dose of 25 mg is the maximal recommended dose. The Applicant is seeking approval of two tablet strengths (25 mg and 50 mg).

The phase 1 program consisted of 29 clinical studies that included: 6 biopharmaceutic (bioavailability, food effect and in vitro-in vivo correlations studies) studies and 23 human pharmacokinetic studies (18 studies that evaluated the extended release formulation and 5 studies that evaluated an oral solution or immediate release tablet). The five initial clinical studies used the immediate release formulation, and the rest used the to-be-marketed formulation (extended release). The terminal elimination half-life of mirabegron was determined to be approximately 50 hrs. Time to maximum concentration (Tmax) was reached in approximately 3.5 hrs. In addition to the standard pharmacokinetic studies, the sponsor also conducted two thorough QT studies (178-CL-037 and 178-CL-077).

As the target population of patients with overactive bladder is likely to be older, the Applicant performed studies to characterize the pharmacokinetics of mirabegron in special populations including the elderly, those with renal impairment and those with hepatic impairment. The Applicant also conducted a total of 10 drug-drug interaction

studies that evaluated potential interactions with mirabegron based on in vitro transporter and metabolism studies and the potential for concomitant use of agents in the intended patient population. Clinical Pharmacology findings included:

- Based on the phase 3 clinical trials of mirabegron, dosing was done on-demand without regard to food. Therefore, although Cmax and AUC of mirabegron were reduced by intake of a low fat meal, these fluctuations from intake of different foods are not expected to affect safety or efficacy, and no restrictions on food intake was required for labeling purposes.
- Based on phase 1 clinical trials of mirabegron, the following dose modification recommendations were made by the Clinical Pharmacology review team:
    - Renal impairment: No dose adjustment for patients with moderate renal impairment, but those with severe renal disease should use the 25 mg dose. Patients with End stage renal disease should not use mirabegron.
    - Hepatic impairment: A maximum dose of 25 mg is recommended for patients with moderate hepatic impairment. Patients with severe hepatic impairment should not use mirabegron
- Other clinical pharmacology studies reported the following special population information:
    - Geriatric use: There was no significant difference in mirabegron exposure in relation to age (18-55 years versus 65-80 years). Therefore, no dose adjustment for elderly patients (65 and older) was recommended by the Clinical Pharmacology review team
    - Gender: The exposure was approximately 40-50% higher in females compared to males, but when corrected for body weight, the difference between genders is only approximately 20-30%. Phase 3 studies were conducted in men and in women, with no evidence of different safety between the genders. Therefore, the Clinical Pharmacology and Clinical review teams concurred that there was no need for dose adjustment based on gender.
    - The QT study did not identify a major signal of clinical concern, although increases approaching the designated threshold of concern were observed in the QT interval in females at the 200 mg dose. The Clinical and Interdisciplinary QT team agreed that there was no significant QTc prolongation effect reported for mirabegron.
- Key clinical pharmacology studies identified the following issues:
    - Mirabegron increased blood pressure and heart rate in a dose-dependent manner. Data from these clinical studies were further evaluated by the Division of Cardiorenal Products and the Pharmacometrics Group (For additional details on the analysis of these signals, see Section 8 of this review)
    - Mirabegron may be a CYP2D6 inhibitor. Labeling will need to indicate that caution should be used when mirabegron is co-administered with a medication significantly metabolized by CYP2D6 that has a narrow therapeutic index.

Comments:

1. *Drug-drug interactions studies were reviewed by the Clinical Pharmacology team. The Clinical Pharmacology team concluded that the two dosage strengths (25 mg and 50 mg) and dosage regime (without regard to food intake), proposed by the Applicant, were acceptable. In addition, results of extrinsic and intrinsic factor studies (such as alcohol intake, hepatic and renal impairment), and drug-drug interaction studies will be labeled where appropriate.*
2. *The Clinical Pharmacology reviewer also evaluated whether any changes in the pharmacokinetics occurred in the elderly and concluded no dose adjustment was necessary for geriatric patients or by gender.*

On January 24, 2012, the Interdisciplinary Review Team (IRT) for QT Studies provided a consult regarding the Applicant's thorough QT study (178-CL-077) and made the following recommendation, "No significant QTc prolongation effect of mirabegron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

Comment: Of note, the original thorough QT study results were reviewed under IND 69,416 and found to be insufficient to adequately characterize the magnitude of the effect of mirabegron on QTc because it was not powered by gender (See IRT QT review dated March 3, 2010). I concur with the IRT review team that Study 178-CL-077 was sufficient to demonstrate that there was no serious QT signal of concern was identified at the proposed doses of mirabegron.

The Clinical Pharmacology review team made the following recommendation in their review dated May 22, 2012, that, "From the Clinical Pharmacology perspective this NDA is acceptable." No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team.

Comment: I concur with the approval recommendation of the Clinical Pharmacology review team. There are no outstanding Clinical Pharmacology issues.

6. Clinical Microbiology

A consult to the Product Quality Microbiology group was requested to provide advice on the Applicant's proposed microbial limits testing. The Microbiology reviewer completed his consult on March 9, 2012. The consult stated that the Applicant's amendment to address microbial limits testing was acceptable and, "…the NDA is now recommended for approval on the basis of product quality microbiology."

Comment: I concur with the approval recommendation of the Microbiology Review team that there are no outstanding issues related to microbial specifications.

7. Efficacy/Statistics

The pivotal analysis set included efficacy data from the three Phase 3 trials (178-CL-046, 178-CL-047 and 178-CL-074). These three phase 3 trials provided the primary evidence for efficacy of mirabegron for the treatment of overactive bladder. In these trials, three oral daily doses of mirabegron were evaluated, 25 mg, 50 mg and 100 mg. Of these doses, the Applicant requested consideration of only two doses in this submission: 25 mg and 50 mg. Therefore, the focus of the clinical efficacy review centered on the findings from these two doses.

The designs of these three phase 3 clinical trials were highly similar in that all were double-blind, placebo-controlled, multinational trials and had a pre-specified treatment period of 12 weeks. After screening, each subject began with a 2 week run-in period. On completion of the run-in period, subjects meeting the inclusion criteria were randomized to one of the mirabegron treatment groups or a placebo control group. Eligible patients experienced frequency of micturition on average $\geq$ 8 times per 24-hour period during the 3-day micturition diary period and at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during the 3-day micturition diary period. The similarity in design across these phase 3 trials allowed analyses to be performed both by individual study and after pooling data from all three trials.

In January 2008, following submission of phase 3 study protocols for special protocol assessment (SPA), the Division provided the Sponsor with Phase 3 protocol review comments which recommended that a 25 mg dose of mirabegron be evaluated. The Applicant subsequently included a 25 mg dose group in study 178-CL-074.

One trial (178-CL-046) included an active control group that the Applicant stated was to provide additional treatment data from an approved OAB product (tolterodine SR 4 mg daily) to allow comparison of effect size to mirabegron treatment.

Comment: Trial 178-CL-046 was not designed as a comparative superiority trial (b) (4) [redacted]

A brief overview of the three primary clinical trials is outlined in the table below:

Table 1 - Overview of pivotal phase 3 trials*:

Trial #	Objective	Design and control type	Test products, dose regimen and administration route	Subject numbers and type	Duration of Treatment
178-CL-046 in Europe and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg, or matching placebo po; once daily with or without food	1987 Adults with OAB	2-week run-in followed by 12-week double blind treatment period
178-CL-047 in Canada, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg or matching placebo po; once daily with or without food	1329 Adults with OAB	2-week placebo run-in followed by 12-week double blind treatment period
178-CL-074 in Canada, Europe and United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg or matching placebo po; once daily with or without food	1306 Adults with OAB	2-week placebo run-in followed by 12-week double blind treatment period

*Adapted from Table 2 of the Medical Officer's review dated June 1, 2012.

Comment: The population studied in these phase 3 trials was determined by the clinical and statistical review teams as sufficient for the purposes of efficacy review.

All subjects enrolled in the three Phase 3 trials included a 2 week single-blind placebo run-in period followed by a 12-week double blind treatment period. Subjects were instructed to complete the 3-day micturitions diary before each visit in the run-in and treatment periods. Times of micturition, voided volume (2 of 3 days), urgency severity, incontinence episodes and pad use were recorded in the micturition diary.

The co-primary efficacy endpoints for these phase 3 trials were change from baseline to Treatment Week 12 (end of trial) in:

1. Mean number of incontinence episodes per 24 hours as compared to placebo based on a 3-day micturition diary and;
2. Mean change from baseline to endpoint in the mean number of micturitions per 24 hours as compared to placebo based on a 3-day micturition diary

Key secondary endpoints that were also evaluated included: volume voided per micturition, number of incontinence episodes per 24 hours at Week 4 and number of

micturitions per 24 hours at Week 4. Primary and key secondary efficacy results from these three trials were analyzed by both individual trial and also pooled analysis.

Efficacy data were analyzed using the following datasets:

- Full analysis set (FAS): all randomized subjects who took at least one dose of double-blind study medication and had a micturition measurement in the baseline diary and at least one post-baseline visit diary with a micturition measurement.
- FAS incontinence (FAS-I): all randomized subjects who took at least one dose of double-blind study medication and had a micturition measurement and at least one incontinence episode in the baseline diary and at least one post-baseline diary with a micturition measurement.

In the three phase 3 studies, mirabegron was evaluated in a total of 4,285 subjects in the FAS and 2815 in the FAS-I.

Comment: The trial protocols did not require a minimum number of incontinence episodes for inclusion of a subject into a study. Therefore, for analysis of the endpoint of mean number of incontinence episodes, the FAS-I population was analyzed and for evaluation of the mean number of micturitions, the total FAS population was analyzed.

Key inclusion – exclusion criteria for the pivotal phase 3 trials:

Key entry criteria for the three phase 3 trials (178-CL-046, 178-CL-047 and 178-CL-074) in common included:

- Adults (female and male) with overactive bladder symptoms (urinary frequency and urgency with or without incontinence) for at least 3 months prior to enrollment
- Frequency of micturition on average ≥ 8 times over 24 hours during the 3-day diary run-in period
- At least 3 episodes of urgency (Grade 3 or 4) with or without incontinence as documented during the 3-day diary run-in period

Both subjects who were antimuscarinic treatment naive and subjects who received prior OAB antimuscarinic therapy could be enrolled.

Demographics and characteristics across the pivotal phase 3 trials:

Subjects in the mirabegron development program were comparative to those patients with OAB population that would receive the product in the US after approval, although the majority of subjects in these pivotal studies reported their ethnicity as white. Subjects in the efficacy (FAS) and FAS-I populations were predominantly female and reported their ethnicity as white across the phase 3 trials. The mean age and distribution of patients ≥ 65 were similar across the primary phase 3 studies. A brief summary of key demographics in these studies is outlined in the table below:

Table 2 – Summary of key demographic characteristics*:

Category	178-CL-046		178-CL-047		178-CL-074	
	FAS	FAS-I	FAS	FAS-I	FAS	FAS-I
	N=1906	N=1165	N=1270	N=993	N=1251	N=773
Gender						
Male	534(28.0%)	193 (16.6%)	320 (25.2%)	168(18.0%)	394 (31.5%)	158(20.4%)
Female	1372 (72%)	972 (83.4%)	950 (74.8%)	765 (82.0%)	857(68.5%)	615(79.6%)
Age						
Mean(SD)	59.1(12.4)	60.0(12.1)	60.2(13.4)	61.1(13.3)	59.1(3.0)	60.0(12.6)
Race						
White	1891(99.2%)	1153(99.0%)	1120(88.2%)	830 (89.0%)	1134(90.6%)	696 90.0%)
Black	6 (0.3%)	5 (0.4%)	108 (8.5%)	78 (8.4%)	96 (7.7%)	65 (8.4%)
Asian	5 (0.3%)	4 (0.3%)	23 (1.8%)	11 (1.2%)	16 (1.3%)	10 (1.3%)
Other	4 (0.2%)	3 (0.3%)	19 (1.5%)	14 (1.5%)	5 (0.4)%	2 (0.3%)
BMI (kg/m2)						
<25	592 (31.1%)	332 (28.5%)	307 (24.2%)	216 (23.2%)	317 (25.3%)	181(23.4%)
25-<30	765 (40.2%)	449 (38.5%)	421 (33.2%)	297 (31.8%)	466 (37.3%)	277(35.8%)
≥ 30	548 (28.8%)	384 (33.0%)	541 (42.6%)	420 (45.0%)	468 (37.4%)	315(40.8%)

*Adapted from Table 1 of the Medical Officer's review dated June 1, 2012.

History and baseline characteristics of patients with OAB were also similar across the three pivotal trials in the FAS and FAS-I populations. All three types of OAB were represented including urge incontinence only, mixed stress/urge incontinence with urge as a predominant factor and frequency/urgency without incontinence. Subjects could also be antimuscarinic treatment naïve, have received prior antimuscarinic therapy and/or had previous surgery for overactive bladder prior to enrollment, although concomitant use of medications to treat overactive bladder was an exclusion criteria at screening. Mean duration of OAB symptoms was similar across treatment groups in the FAS, ranging from 85.1 to 88.3 months. The proportion of patients with prior surgery for OAB was also similar across treatment groups in the FAS, ranging from 8.3% to 9.5%. The primary difference between the FAS and FAS-I populations was the higher proportion of females in the FAS-I populations. The Applicant did not identify any clinical differences of concern between treatment groups in terms of demographics or OAB baseline characteristics in the phase 3 trials in the FAS or FAS-I populations.

The Medical Officer stated in his review that, "History and baseline characteristics of OAB were comparable across all treatment groups in the FAS and FAS-I populations…..The population demographics did reflect the patient population who would use the drug clinically post-approval." (See Medical Officer's review dated June 1, 2012)

Comment: I concur with the Medical Officer that the demographic and baseline OAB data from these phase 3 studies would encompass those in the target OAB population for mirabegron.

Subject disposition in the pivotal phase 3 trials:

For Study 178-CL-046, on completion of the run-in period, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1:1 ratio to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine SR 4 mg orally daily for 12 weeks. A total of 2,437 subjects were screened with 2,336 receiving placebo run-in study drug and 1,987 subjects randomized to one of the four treatment groups outlined above. The proportion of subjects who discontinued treatment was similar across treatment groups ranging from 8.9% to 11.5%. The primary reason reported for discontinuation after randomization across all treatment groups was an adverse event and consent withdrawal.

For Study 178-CL-047, on completion of the run-in period, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive placebo, mirabegron 50 mg, or mirabegron 100 mg orally daily for 12 weeks. A total of 2,342 patients were screened with 2,149 patients receiving placebo run-in study drug and 1,329 patients randomized into one of three treatment groups outlined above. The proportion of patients randomized into the double-blind treatment period that discontinued the study was comparable across treatment groups (12.2% to 15.2%).The two most frequently cited reasons for discontinuation were withdrawal of consent and adverse event.

For Study 178-CL-074, on completion of the run-in period, patients meeting inclusion criteria and not meeting exclusion criteria were randomly assigned in a 1:1:1 ratio to receive placebo, mirabegron 25 mg, or mirabegron 50 mg orally daily for 12 weeks. A total of 2,201 patients were screened with 2,030 patients receiving placebo run-in study drug and 1,306 patients randomized into on of three treatment groups outlined above. The proportion of patients randomized into the double-blind treatment period that discontinued the study was comparable across treatment groups (10.6% to 15.2%).The two most frequently cited reasons for discontinuation were consent withdrawal and AEs.

Comment: In his June 1, 2012, review, the Medical Officer reviewed the subject disposition and discontinuation rates for each individual phase 3 trial and determined that completion and discontinuation rates across treatment groups were clinically acceptable and likely did not affect trial outcomes. I concur with the Medical Officer's determination regarding subject disposition in these trials.

Results from the pivotal phase 3 trials:

The statistical review for this NDA was based on the results from three double-blind, randomized, multinational phase 3 trials: 178-CL-046, 178-CL-047 and 178-CL-074. The primary analysis of the co-primary and key secondary endpoints was the FAS and FAS-I populations. Patient exposure to mirabegron included a total of 410 subjects in the FAS population who received the 25 mg dose and 1,324 subjects in the FAS population who received the 50 mg dose in the pivotal trials. Only Study 178-CL-074 evaluated data for the proposed 25 mg dose which was added at the Division's request.

The co-primary efficacy variables were defined as follows:

- Change from baseline to Final Visit (Week 12) in the mean number of incontinence episodes per 24 hours based on a 3 day micturition diary (in subjects with incontinence at baseline)
- Change from baseline to Final Visit (Week 12) in the mean number of micturitions per 24 hours based on a 3 day micturition diary

In all three studies, both co-primary efficacy endpoints were analyzed using an ANCOVA model which included treatment group, gender, geographical region, and baseline measurement. Point estimates and two-sided 95% confidence intervals for the mean change from baseline for the difference in mean change from baseline between each mirabegron treatment group and placebo (and between tolterodine and placebo) were calculated as follows:

- For the change from baseline to end of treatment (final visit) in mean number of micturitions per 24 hours, the pair-wise p-values were derived from the above ANCOVA model for the comparisons between each active treatment group vs. placebo group.
- For the change from baseline to end of treatment (final visit), due to the non-normal data distribution of change from baseline in mean number of incontinence episodes, a stratified rank ANCOVA model was utilized.

If no Week 12 diary data measurements were available (often because the subjects were prematurely discontinued), the last available earlier post-baseline average of the diary data measurements within a designated visit window and post-dosing window was used as the final visit measurement (LOCF methodology).

In each of the three studies, the Applicant adopted a stepwise parallel gate-keeping procedure to control the type I error rate over multiple active treatment groups and multiple efficacy endpoints at the 0.05 significance level. This stepwise parallel gate keeping procedure was performed to control the Type I error rate at the 0.05 significance level for the coprimary and key secondary efficacy endpoints. Since 2 mirabegron treatment groups (50 and 100 mg for 178-CL-046 and 178-CL-047; 25 and 50 mg for 178-CL-074) were compared with placebo, the Hochberg procedure was used to adjust for multiplicity and control the overall Type I error within each stage.

The Applicant also pooled the primary efficacy analysis study results and presented the co-primary efficacy endpoints as adjusted mean changes from baseline to final visit for the 50 mg and 100 mg doses. As only Study 178-CL-074 included the mirabegron 25 mg dose, this dose was not included in the pooled primary efficacy analysis calculations.

Comment: The Medical Officer stated that although pooled data provides an overview of mirabegron efficacy at all doses studied, as all mirabegron doses in each of the pivotal studies were clinically and statistically superior to placebo, data from the individual studies will be presented in labeling (See Medical Officer review dated June 1, 2012). I concur that presentation of individual studies as opposed to pooled efficacy, in light of the fact that the efficacy of the 25 mg dose was only tested in 178-CL-074, is necessary

for labeling purposes. Therefore, this review will focus on the individual efficacy results from Studies 178-CL-046, 178-CL-047 and 178-CL-074.

Analyses for Studies 178-CL-046, 178-CL-047 and 178-CL-074 are outlined below:

Table 3: Summary of Primary Efficacy Analyses- 178-CL-046*

	Placebo	Mirabegron 50 mg	Mirabegron 100 mg	Tolterodine SR 4 mg
Mean number of Incontinence Episodes per 24 hours (FAS-I) at final visit				
N	291	293	281	300
Mean	1.54	1.22	1.37	1.42
Change from Baseline**	-1.17	-1.57	-1.46	-1.27
Difference vs placebo (p-value†)		-0.41(0.003#)	-0.29(0.010#)	-0.10(0.115)
Mean number of Micturitions per 24 hours (FAS) at final visit				
N	480	473	478	475
Mean	10.35	9.70	9.76	9.97
Change from baseline*	-1.34	-1.93	-1.77	-1.59
Difference vs, placebo (p-value‡)		-0.60 (<0.001#)	-0.44(0.005#)	-0.25(0.112)

*Table 3 adapted from Table 9 in the Statistical review dated June 7, 2012
**Change from baseline was obtained from an ANCOVA model
†Nominal P P-values were from pair-wise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡Nominal P-values were from pair-wise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior to placebo with multiplicity adjustments at the 0.05 level

Table 4: Summary of Primary Efficacy Analyses- 178-CL-047*

	Placebo	Mirabegron 50 mg	Mirabegron 100 mg
Mean number of Incontinence Episodes per 24 hours (FAS-I) at final visit			
N	325	312	296
Mean	1.81	1.33	1.14
Change from Baseline**	-1.13	-1.47	-1.63
Difference vs placebo (p-value†)		-0.34(0.026#)	-0.50 (<0.001#)
Mean number of Micturitions per 24 hours (FAS) at final visit			
N	433	425	412
Mean	10.51	10.09	9.91
Change from baseline*	-1.05	-1.66	-1.75
Difference vs, placebo (p-value‡)		-0.61(0.001#)	-0.70(<0.001#)

*Table 4 adapted from Table 10 in the Statistical review dated 2012
**Change from baseline was obtained from an ANCOVA model
†Nominal P P-values were from pair-wise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡Nominal P-values were from pair-wise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior to placebo with multiplicity adjustments at the 0.05 level

Table 5: Summary of Primary Efficacy Endpoints- 178-CL-074*

	Placebo	Mirabegron 25 mg	Mirabegron 50 mg
Mean number of Incontinence Episodes per 24 hours (FAS-I) at final visit			
N	262	254	257
Mean	1.54	1.21	1.13
Change from Baseline**	-0.96	-1.36	-1.38
Difference vs placebo (p-value†)		-0.40(0.005#)	-0.42(0.001#)
Mean number of Micturitions per 24 hours (FAS) at final visit			
N	415	410	426
Mean	10.33	10.02	10.04
Change from baseline*	-1.18	-1.65	-1.60
Difference vs, placebo (p-value‡)		-0.47(0.007#)	0.42(0.015#)

*Table 5 adapted from Table 11 in the Statistical review dated 2012
**Change from baseline was obtained from an ANCOVA model
†Nominal P P-values were from pair-wise comparisons vs. placebo within the stratified rank analysis of covariance (ANCOVA).
‡Nominal P-values were from pair-wise comparisons vs. placebo within the ANCOVA model.
#Statistically significantly superior to placebo with multiplicity adjustments at the 0.05 level

In summary, the efficacy results from the three phase 3 studies demonstrate:

- Both the mirabegron 25 mg and 50 mg doses demonstrated superiority to placebo for the co-primary endpoints of reduction in the mean number of incontinence episodes per 24 hours and reduction of the mean number of micturitions per 24 hours.
- Mirabegron 50 mg demonstrated a statistically significant reduction in mean number of incontinence episodes and a significant decrease in micturitions for 24 hours as early as Week 4 compared with placebo after multiplicity adjustment.
- Mirabegron 25 mg demonstrated a statistically significant reduction in mean number of incontinence episodes and significant decrease in micturitions at Week 8 compared with placebo after multiplicity adjustment.

Clinical review of the secondary efficacy endpoints (including evaluation of mean volume voided) obtained from the three phase 3 trials and data from the long-term trial (Study 178-CL-049) also supported efficacy of the 25 mg and 50 mg doses of mirabegron for OAB. Although the clinical review team did note that there were some differences reported between the 25 mg and 50 mg dose in terms of secondary efficacy endpoints, and the time to onset of the statistically significant primary efficacy endpoint changes, at 8 weeks of treatment, the observed benefit of 25 mg and 50 mg appeared comparable.

Statistical review of the primary efficacy results for the pivotal phase 3 trials:

The statistical review for this NDA was primarily based on the three double-blind phase 3 studies, 178-CL-046, 178-CL-047 and 178-CL-074. The statistical reviewer stated that there were no statistical issues identified in this submission. In a review dated June 7, 2012, the statistical reviewer stated that, "From a statistical perspective, all doses of mirabegron (25 mg, 50 mg and 100 mg) are effective in treating overactive bladder. Although mirabegron 50 mg is the proposed dose for general OAB patients by the Applicant, mirabegron 25 mg dose also showed very similar efficacy on the co-primary endpoints compared to mirabegron 50 mg dose in one Phase 3 trial with adequate sample size. Therefore, mirabegron 25 mg dose should be considered for general OAB patients as well."

Comment: I concur with the Statistical review team that the 25 and 50 mg doses have demonstrated efficacy through Studies 178-CL-046, 178-CL-047 and 178-CL-074. Although supportive efficacy results for the 50 mg dose were obtained from the long-term extension study (178-CL-049), these data were not reviewed by the clinical and statistical teams for efficacy claims because of the lack of a placebo control.

Other Efficacy Issues:

The use of the 25 mg dose as a starting dose was extensively discussed during the NDA review cycle. The efficacy of the 25 mg dose was supported in Study 178-CL-074 and the determination that there were statistically significant and clinical relevant differences from baseline and from placebo for mirabegron 25 mg at Weeks 8 and 12. A detailed discussion of the rationale for the proposed initial dose of 25 mg is outlined in the Medical Officer review dated June 1, 2012.

The Medical Officer summarized his findings regarding the 25 mg dose of mirabegron as a starting dose as follows, "Taken all information together, the results for mirabegron 25 mg and 50 mg appear similar at 8 weeks for the primary efficacy endpoints. However, it would appear that mirabegron 50 mg may offer an overall better clinical benefit. Therefore, in order to optimize the risk/benefit ratio, a starting dose of 25 mg for all patients, with an 8 week trial, followed by an increase to mirabegron 50 mg in patient with suboptimal improvement in symptoms seems reasonable The 25 mg dose should also be utilized in patients with moderate hepatic or severe renal impairment. The CDTL review dated June 26, 2012, included the following additional comments regarding the proposed 25 mg starting dose, "In regard to dose selection, taken together, the data demonstrates benefit for both doses at Week 4, and similar primary efficacy results for mirabegron 25 mg and 50 mg at Week 8, but there is evidence for greater overall clinical benefit for mirabegron 50 mg compared to 25 mg. Therefore, in order to optimize the risk/benefit ratio, a starting dose of 25 mg for all patients, followed by an increase to mirabegron 50 mg in patients with suboptimal improvement in symptoms seems reasonable and appropriate. The prescriber should be aware that it may take up to 8 weeks to achieve optimal results with mirabegron 25 mg."

Comment: I concur with the Medical Officer and CDTL that there is adequate rationale for the 25 mg starting dose and increasing to the 50 mg dose from a clinical efficacy perspective after an 8 week trial. I also concur with the CDTL that the prescriber should be made aware, through labeling, of timeframe required to achieve optimal efficacy results with mirabegron 25 mg dose. Final labeling for mirabegron will reflect the optimal timeframe for use of the 25 mg dose.

The clinical review team also evaluated a Phase 2 study (178-CL-060) that evaluated the effect of mirabegron on bladder emptying in men with lower tract symptoms and bladder outlet obstruction to demonstrate lack of a detrimental effect on bladder function in men. After review of this study, the Medical Officer concluded that, "This study does not include sufficient numbers of subjects with long enough duration of treatment (b) (4) in patients with bladder outlet obstruction (BOO). At the time same, it raises no particular concern and provides some degree of comfort in the event of use in men with latent BOO." (See Medical Officer review dated June 1, 2012).

The clinical review team also evaluated the pooled efficacy analysis of the phase 3 studies, key secondary efficacy endpoints (including mean volume voided per micturition, nocturia, OAB-q Bother Score), the persistence of efficacy, efficacy in subpopulations including by each gender, by race, and by age.

Comments: Findings from evaluations of these subpopulations were incorporated into labeling where appropriate. I also concur with the Medical Officer's conclusion that study 178-CL-060 (b) (4)

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate that Myrbetriq (mirabegron) was effective in the treatment of overactive bladder. The Medical Officer summarized efficacy results in his June 1, 2012, review as follows, "All mirabegron doses in each of three pivotal studies were clinically and statistically superior to placebo for the co-primary endpoints. The efficacy of the 25 mg mirabegron dose was tested only in Study 178-CL-074….. Efficacy data from individual studies, not pooled efficacy data, will be used in labeling."

In his review dated, June 26, 2012, the CDTL further concluded that, "In three, randomized, double-blind, 12-week, placebo-controlled studies, mirabegron 50 mg demonstrated efficacy in the treatment of OAB, as demonstrated by success on the co-primary endpoints and most of the secondary endpoints. In Study 178-CL-074, mirabegron 25 mg also demonstrated efficacy for the treatment of OAB. The treatment effect for both doses is highly statistically significant compared to placebo and based upon a number of secondary endpoints and secondary analyses, the effect of mirabegron on OAB is considered to be clinically meaningful."

Based on the submitted efficacy results from the submitted three adequate and well-controlled trials (178-CL-046, 178-CL-047 and 178-CL-074) for mirabegron, I agree with the reviewers and CDTL that it is reasonable to conclude that the proposed Applicant's product will be efficacious for the treatment of overactive bladder. Therefore, I concur with the recommendations of the clinical review team, statistical review team and Cross-Discipline Team Leader that there are no outstanding efficacy concerns for this new product.

8. Safety

The safety data for Myrbetriq (mirabegron) to support once daily use for the treatment of overactive bladder were primarily derived from the 41 clinical studies and postmarketing data available from Japan contained in this NDA submission. The safety analysis concentrated on results from several patient cohorts including: 1) the three pivotal phase 3 studies designated the EU/NA Phase 3 Population (including Studies 178-CL-046, 178-CL-047 and 178-CL-074), 2) the long-term (52 week) extension study designated as the EU/NA Long-term Controlled Population (Study 178-CL-049) and 29 phase I studies that included one key thorough QT studies (178-CL-077) and other drug-drug interaction studies (including Studies 178-CL-038 [desipramine] and 178-CL-036 [ketoconazole]). An additional phase 2 study (178-CL-060), double-blind, placebo controlled study that evaluated the urodynamics and safety of mirabegron in male subjects with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) was submitted and reviewed solely for purposes of safety to determine if there was a detrimental effect of mirabegron in men with bladder outlet obstruction.

The safety database consists of a total of over 5,000 subjects who were exposed to at least one dose of Myrbetriq (mirabegron) in the clinical development program. Of these subjects:

- 1,462 received mirabegron in phase 1 studies.

- 2,736 received mirabegron in the principal controlled Phase 3 population
- 1,632 subjects with overactive bladder (OAB) received mirabegron at either 50 mg or 100 mg in the one year long-term extension study (178-CL-049)

Several safety populations that were evaluated by the clinical reviewers to assess the safety of mirabegron were defined as follows:

1. The EU/NA 12 week Phase 3 population (referred to in this section as the pivotal phase 3 trials) which consisted of the phase 3 trials (178-CL-046, 178-CL-047 and 178-CL-074) submitted to support efficacy in the OAB population.
2. The Global OAB 12-week Phase 2/3 population which consisted of 6 placebo-controlled double-blind studies in patients with different indications including lower urinary tract obstruction/bladder outlet obstruction and type 2 diabetes.
3. The Global Phase 2/3 population – which consisted of 12 studies in patients who received at least one dose of mirabegron in a phase 2 or 3 study for any indication
4. The EU/NA long-term controlled population – consisted of all subjects who enrolled in the 1- year study double blind phase 3 study in patients with OAB (178-CL-049). Patients who completed 178-CL-046 or 178-CL-047 as well as treatment naïve patients who met the inclusion/exclusion criteria could be enrolled.

Comment: The focus of the safety review for this application was on the EU/NA 12 week Phase 3 population of the three pivotal trials and also included the safety database with the longest duration – the EU/NA long-term controlled population (Study 178-Cl-049). This safety database specifically evaluated the to be marketed formulation in the intended population. Other safety databases, such as the Global 2/3 database contained studies using dose forms that were different then those in the EU/NA trials and also included studies of different patient populations. However, all safety databases, including the Global 12 OAB 12-week Phase 2/3 population were reviewed to provide additional safety information as needed by the review team.

Pivotal phase 3 trial population (178-CL-046, 178-CL-047 and 178-CL-074):

The primary safety analysis focused on the pivotal phase 3 trial population, which used the to be marketed mirabegron tablets and included a total of 2,736 subjects. Of these subjects, 1380 used placebo, 432 used mirabegron 25 mg, 1375 used mirabegron 50 mg, 929 used mirabegron 100 mg and 167 used mirabegron 200 mg. There were also 495 subjects who received tolterodine ER 4 mg in active comparator arms.

Long-term extension study (178-CL-049):
This was a 52 week long term safety study of two doses of mirabegron with an active comparator arm. Patients were randomized to 3 treatment arms on a 1:1:1 basis. The treatment arms were mirabegron 50 and 100 mg once a day, and tolterodine extended release (ER) 4 mg once a day. In this study, 812 subjects received mirabegron 50 mg once daily, 820 subjects received mirabegron 100 mg once daily and 812 received

tolterodine 4 mg once daily. Of the 16,32 subjects who received either mirabegron 50 mg or 100 mg, 901 were new exposures and 721 were re-exposures.

The Medical Officer reviewed the total population exposure data in his review dated June 1, 2012, and stated that, "The overall patient exposure to mirabegron and duration of exposure far exceeds ICH Guidance criteria for a new molecular entity, and is adequate to estimate safety of mirabegron at the to be marketed doses."

Comment: I concur with the Medical Officer that the safety database was sufficient to support approval of mirabegron.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events in the three pivotal phase 3 studies (178-CL-046, 178-Cl-047 and 178-CL-074) and long-term extension study (178-CL-049):

Deaths: There were 3 deaths in the phase 3 pivotal phase 3 studies and 5 deaths in the long-term 1-year extension study. An additional death occurred in a patient completing an extension trial in Japan. All nine deaths were reviewed by the Applicant's Cardiovascular Adjudication Committee. Of the 8 deaths, 1 was in a subject treated with placebo, and 3 in subjects using tolterodine. None of the deaths were considered by the Applicant or the clinical review team to be related to mirabegron.

Non-fatal Serious Adverse Events (SAE):

In the pivotal phase 3 trials, one or more SAEs were reported for 62/2736 (2.3%) mirabegron, 29/1380 (2.1%) placebo and 11/495 (2.2%) tolterodine patients, with no apparent mirabegron dose response. The most common SAEs in the total mirabegron group (including 25 mg, 50 mg and 100 mg doses) were atrial fibrillation (mirabegron: 5/2736 [0.2%]; placebo: 1/1380 [0.1%]; tolterodine: 0/495), and chest pain (mirabegron: 4/2736 [0.1%]; placebo: 2/1380 [0.1%]; tolterodine: 0/495.)

In the EU/NA long-term Controlled Population (178-CL-049), one or more SAE was reported by 93/1632 (5.7%) mirabegron patients (mirabegron 50 mg: 42/812 [5.2%]; mirabegron 100 mg: 51/820 [6.2%]) and 44/812 (5.4%) tolterodine patients. The most common SAE in the total mirabegron group (including both the 50 mg and 100 mg doses) were osteoarthritis (mirabegron: 3/1632 [0.2%]; tolterodine: 1/812 [0.1%]) and cerebrovascular accident (mirabegron: 3/1632 [0.2%]; tolterodine: 1/812 [0.1%]). Other findings of note from the long-term study included 11 reports of neoplasms (report in the SOC as Neoplasms, benign, malignant or unspecified) reported in the mirabegron 100 mg group as compared to 4 neoplasms in SOC from the tolterodine group and 1 in the SOC from mirabegron 50 mg group.

Discontinuations for adverse events:

In the pivotal phase 3 trials, the most common adverse events (by Preferred Term) leading to permanent discontinuation of drug in the total mirabegron group were:

constipation (mirabegron: 6/2736 [0.2%]; placebo: 3/1380 [0.2%]; tolterodine: 1/495 [0.2%]), headache (mirabegron: 6/2736 [0.2%]; placebo: 5/1380 [0.4%]; tolterodine: 2/495 [0.4%]) and hypertension (mirabegron: 6/2736 [0.2%]; placebo; 2/1380 [0.1%]; tolterodine: 1/495 [0.2%]). The most frequent adverse events leading to discontinuation in the pivotal phase 3 trials for the 25 mg and 50 mg dose were nausea (0.2%), headache (0.2%) and hypertension (0.2%).

In the EU/NA Long-term Controlled Population, the most common TEAEs (by PT) leading to permanent discontinuation of study drug in the total mirabegron group were constipation (mirabegron: 9/1632 [0.6%]; tolterodine: 0/812), headache (mirabegron: 9/1632 [0.6%]; tolterodine: 3/812 [0.4%]), dizziness (mirabegron: 6/1632 [0.4%]; tolterodine: 0/812) and hypertension (mirabegron: 6/1632 [0.4%]; tolterodine: 3/812 [0.4%]).

Comments:

1. *The Medical Officer and CDTL reviewed narratives of fatal and non-fatal serious adverse events and discontinuations and agreed that there were no events that raised new safety concern or imbalances that indicated new safety trends in the pivotal phase 3 or long-term safety databases. I concur with their assessments.*
2. *In all atrial fibrillation adverse events, confounding factors that could incite atrial fibrillation were present. I concur with the CDTL and Medical Officer that the small number of cases and confounding factors, precludes attribution of atrial fibrillation to mirabegron.*
3. *Regarding the increased reports of neoplasms in the mirabegron 100 mg group in Study 178-CL-049 (long-term extension study): In the Medical Officer's review (dated June 1, 2012), the clinical reviewer stated that he had identified a small difference between mirabegron and placebo in total number of neoplasms when a variety of tumors (mostly reported by one subject each) were added together. This finding was reviewed and sent for further internal oncologic consultation and discussed at the April, 2012, Advisory Committee. A more detailed discussion of this safety finding is addressed in a section below entitled, "Other Significant Safety Issues" in this review.*

Treatment Emergent Adverse Events (TEAEs)

In the pivotal phase 3 trials, the most frequent TEAEs reported by ≥3.0% of patients were hypertension 200/2736 (7.3%) of mirabegron patients versus 105/1380 (7.6%) placebo patients, nasopharyngitis 94/2739 (3.4%) versus 35/1380 (2.5%) and UTI 83/2736 (3.0%) versus 25/1380 (1.8%) for placebo. An overview of the rates of adverse events seen in the pivotal trials is outlined in Table 6 below:

Table 6: Percentages of subjects with adverse events (Regardless of Causality), exceeding placebo and reported by 1% or more in those treated With mirabegron 25 mg or 50 mg in the pivotal phase 3 trials

	placebo (%)	mirabegron 25 mg (%)	mirabegron 50 mg (%)
Number of Patients	**1380**	**432**	**1375**
Hypertension	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Fatigue	1.0	1.4	1.2

In the long term extension study (178-CL-049), the most commonly reported adverse events (>3% of mirabegron 50 mg treated patients), regardless of causality, were hypertension, urinary tract infection, headache, and nasopharyngitis. An overview of the adverse events reported in > 2% of subjects treated with mirabegron 50 mg is outlined in Table 7 below:

Table 7: Percentages of subjects with adverse events (regardless of causality) reported by greater than 2% of subjects treated with mirabegron 50 mg in the long-term extension trial

	mirabegron 50 mg (%)	tolterodine 4 mg (%)
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

Comment: After review of the adverse event data from the pivotal phase 3 trials (178-CL-046, 178-CL-047 and 178-CL-074) and the long term extension study (178-CL-049), the

Medical Officer and CDTL concluded that the commonly reported adverse events reported in the long-term safety study were similar to those reported in the short-term studies. IN addition, the most commonly reported adverse events related to mirabegron were reported at only modestly higher rates compared to placebo. These rates provided further support that the safety profile for mirabegron was acceptable.

Vital Sign Findings

Mirabegron is classified from a pharmacologic standpoint as a beta adrenergic agonist and was expected to increase heart rate and potentially also increase blood pressure. The clinical review team performed focused reviews on heart rate and blood pressure changes.

- Heart rate changes: In the pivotal phase 3 population, the adjusted mean difference compared to placebo for change from baseline in patients receiving mirabegron 25 mg, 50 mg, 100 mg and tolterodine was 0.9, 1.0, 1.9 and 1.0 bpm for AM measurements, respectively, and 0.6, 1.0, 2.3 and 2.1 bpm for PM measurements, respectively. The adjusted mean change from baseline pulse rate in the long-term extension study (178-CL-049) for mirabegron 50 mg, 100 mg and tolterodine groups was 0.9, 1.6 and 1.5 bpm for AM measurements, respectively, and 0.4, 1.3 and 1.9 bpm for PM measurements, respectively.

  The Medical Officer evaluated the data on changes in pulse rate in the safety databases and concluded, "In Phase 3 studies, the to-be-marketed dose of 50 mg appears to be associated with a heart increase of 1 bpm. The mirabegron-related increase in heart rate was higher in Phase 1 studies. The increase in heart rate secondary to mirabegron appears to be modestly greater in women compared to men, and in younger compared to older patients. The mirabegron-related increase in heart rate is not, of itself, a safety concern."

Comment: I concur with the Medical Officer that the finding of an increase in heart rate of approximately 1 bpm in the phase 3 population, similar to that observed with a comparator product (tolterodine) is not, in itself, a safety concern. However, although the changes were modest in the phase 1 and 3 studies, the totality of the vital sign data, specifically systolic and diastolic blood pressure changes, were reviewed in detail as outlined below.

- Blood pressure changes: In the pivotal phase 3 population, 50 mg of mirabegron was associated with an approximate 1 mmHg adjusted mean difference for change from baseline in SBP/DBP compared with placebo. Findings from the phase 3 studies included:
  - Change in SBP from baseline compared to placebo in the pivotal phase 3 population (adjusted mean difference) for mirabegron 25, 50 and 100 mg and tolterodine was -0.6, 0.7, 0.2 and -0.4 mm Hg for AM measurements, respectively, and -1.0, 0.5, 0.9 and 0.0 mm Hg for PM measurements, respectively.

- Change from DBP from baseline compared to placebo in the pivotal phase population (adjusted mean difference) for mirabegron 25, 50 and 100 mg and tolterodine was -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements, respectively, and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.

Additional data on blood pressure changes for mirabegron was obtained in a phase 1 thorough QT study [178-CL-077). In Study 077, the TQT study in 352 healthy volunteers (mean age 33 years), at hour 3 on the final study day, mean SBP/DBP increases in mirabegron 50 mg subjects compared to placebo subjects were 4.0/1.6 mm Hg. Similar blood pressure increases were reported in study 178-CL-031 with the 50 mg dose of mirabegron.

The clinical review team raised concerns about the clinical significance of these mirabegron associated changes in blood pressure and consulted to the Division of Cardiorenal Products (DCRP). Input from the Reproductive Health Advisory Committee was also sought regarding these changes.

Comment: More extensive discussion of this potential safety finding of increased blood pressure is included in a section below entitled, "Other Significant Safety Issues" in this review.

Laboratory Findings

The Medical Officer performed a focused evaluation of marked laboratory abnormalities in different subject cohorts including the pivotal phase 3 population (178-CL-046, 178-CL-047 and 178-CL-074) and the long term extension trial (178-CL-049). This safety evaluation included evaluation of mean changes in hematology and chemistry parameters. In his June, 1, 2012, review, the Medical Officer stated that he did not identify any trends of concern related to hematologic values.

- Liver function testing: Based on preclinical findings, changes in liver function possibly causing drug induced liver injury (DILI) were identified as a potential safety issue for mirabegron. The July 2009 guidance entitled, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" outlines that cases of Hy's Law is an ominous indicated of a potential for a drug to cause serious liver injury and is considered predictive of a drug's ability to cause permanent liver injury to patients.

  Therefore, in his June, 1, 2012, review, the Medical Officer outlined the results of his evaluation of trends obtained from liver function testing for possible Hy's Law cases in the pivotal phase 3 trials, long term extension study and the global safety database. One specific analysis focused on potentially clinically significant (PCS) liver function test abnormalities in the pivotal phase 3 population. Other clinical analyses focused on evaluation for cases in the safety database that met the

definition of "Hy's Law" (defined as 3-fold or more transaminase elevation combined with 2-fold or more bilirubin) and reports of hepatic adverse events.

The clinical review team identified two cases that met the Hy's Law definition in the mirabegron development program, and concluded that a causal relationship to mirabegron could not be excluded, although liver function testing from the safety database did not demonstrate a positive trend related to hepatotoxicity. Review of the clinical serum liver function data identified subjects with hepatic laboratory parameters meeting the Applicant's predefined criteria of potentially clinically significant (PCS) as 0.5%, 0.7% and 0.2% in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively. The identified cases that met Hy's Law as well as cases of hepatic adverse events were presented to the Reproductive Health Advisory Committee as a topic on April 4, 2012.

In his June 1, 2012, review, the Medical Officer concluded that, "…questions are thus raised as to whether mirabegron played a role in a few clinically significant hepatic AEs, or whether there is a relationship between mirabegron and liver function test abnormalities in the context of a hypersensitivity reaction. The data is sparse and precludes definitive conclusions in this area."

- QT issues: A dedicated TQT study [Study 178-CL-077] showed that, according to ICH E14 (2005) criteria, mirabegron did not cause individually corrected QT interval (QTcI) prolongation at the proposed therapeutic dose of 50 mg nor at the supratherapeutic dose of 100 mg, a dose which increased Cmax and AUCtau by approximately 2.9 and 2.6 fold relative to the proposed therapeutic dose of 50 mg. At both doses, the upper bound of the 1-sided 95% CI of corrected QT interval (QTc) interval did not exceed 10 msec at any time.

  Both the Medical Officer and the Interdisciplinary Review Team for QT Studies Consultation reviewed the results of the thorough QT study (TQT). The QT review team concluded in their review dated January 24, 2012, that, "No significant QTc prolongation effect of mirabegron was detected in this TQT study." The Medical Officer concurred with the QT review team's assessment.

Comments:

1. *Although there were some members of the Advisory Committee who expressed concerns regarding the two reported hepatic adverse events, after review of the limited data from the available reports, I concur with the clinical review team to describe the liver function test findings from the pivotal clinical trials and a reference to the cases that met Hy's Law in labeling is appropriate. The clinical review team did not identify any other potential safety signals based on findings from laboratory data for mirabegron.*
2. *I concur with the conclusions of the QT review team and Medical Officer that there are no outstanding QT issues.*

Clinically important safety findings from phase 2 study in men with bladder outlet obstruction (178-Cl-060):

The potential for urinary retention and bladder function decompensation in men with lower urinary tract symptoms (LUTS) and known bladder outlet obstruction (BOO) was assessed by post-void residual urine (PVR) and urodynamic parameters in a phase 2 study (Study 178-CL-060). The Medical Officer reviewed the changes in urodynamic parameters, post void residual data and events of urinary retention and concluded that, "This study does not include sufficient numbers of subjects with long enough duration of treatment (b) (4) in patients with bladder outlet obstruction (BOO). At the time same, it raises no particular concern and provides some degree of comfort in the event of use in men with latent BOO." (See Medical Officer review dated June 1, 2012).

In his review dated June 1, 2012, the Medical Officer reviewed the adverse event data from Study 178-Cl-060 and commented that, "In this study, mirabegron in male OAB patients with LUTS/BOO (Lower Urinary Tract Symptoms/Bladder Outlet Obstruction) did not increase the risk of urinary retention or worsening of bladder function. While notable and informative, (b) (4)

Comment: I concur with the Medical Officer that there do not appear to be any new safety trends related to urinary retention or worsening in bladder function in men with OAB who have LUTS or BOO. (b) (4)

Other Significant Safety Issues Identified:

The clinical review team identified specific safety issues during drug development and also during the review of the submission. These issues were discussed with the Applicant and the majority of these were resolved through labeling. Issues that required additional outside consultation included:

1. Potential increased cardiovascular outcomes:

As previously discussed, the clinical review team had concerns related to the findings of increased mean changes in SBP and DBP in the phase 1 and 3 clinical trials with regard to the potentially for such and increase to cause an increase in cardiovascular adverse events. The clinical review team evaluated the incidence of major adverse cardiovascular events (MACE) and adverse events related to hypertension in the Safety Database. The Medical Officer identified few events of MACE in the global safety database (2/4414 for mirabegron compared to 4/2142 for placebo) and the relative risk of occurrence of MACE was 0.24 (95% CI: 0.02, 1.69) for patients receiving mirabegron compared to placebo. However, because increases in blood pressure as reported in the Phase 1 and 3 databases have a potential to increase adverse cardiovascular outcomes across a population, a consult from the Division of Cardiorenal Products (DCRP) was requested to

assess the potential safety impact of the blood pressure changes in patients using mirabegron.

The DCRP consult was completed on January 20, 2012 and stated that DCRP disagreed with the sponsor's conclusion that the small incremental increases in SBP and DBP seen with mirabegron are not associated with an increased cardiovascular risk. The DCRP consultant recommended that the Applicant put the target population into a risk model to predict what the likely impact of the small increases in blood pressure seen in the phase 1/3 studies could be on cardiovascular event rates.

In February, 2012, the Division and DCRP asked for a consultation from the Division of Clinical Pharmacology I, team leader to assist the Division in evaluating the sponsor's proposed analysis of the 10-year model. A teleconference was held to provide recommendations on the risk assessment model and analyses with the Applicant. The Applicant subsequently submitted the data for the modified risk model and their analysis of the data. The Clinical Pharmacology team leader also analyzed the Applicant's safety data and risk model using a Cox Proportional Hazards model. The blood pressure and Cox Proportional Hazard model findings from the phase 1 and 3 safety data was presented at the April, 2012 Reproductive Health Advisory Committee (AC). The majority of the AC members at the meeting expressed some concern that the findings of increased mean blood pressures changes from baseline reported in phase 1 and 3 studies could result in increased cardiovascular outcomes postmarketing.

On June 11, 2012, the Clinical Pharmacology Team leader and DCRP review team completed their review of the Applicant's cardiovascular risk model and concluded that, "The small increases in SBP for the pooled twelve week phase III trials translate into a small increase in the 10-year general CVD risk…The absolute increase in the mean 10-year CVD risk on average is 0.19% and fails to achieve statistical significance." The review also commented that the potential for CVD risk with the lower dose of mirabegron (25 mg) was "very small and comparable to that of placebo."

The Clinical Review team concurred with the Clinical Pharmacology Team leader and DCRP assessment of a potential increased cardiovascular risk with mirabegron use and also with the AC members recommendation to consider additional postmarketing evaluation of this increased blood pressure signal. After the April, 2012, Reproductive Health Advisory Committee meeting, the Division requested a consult from the Division of Epidemiology II to determine the design and conduct of an epidemiology study to further assess this signal.

The Division of Epidemiology II (DEPI) provided input on the design of the postmarketing required study to assess the incidence of potential cardiovascular outcomes. DEPI and the Division met and discussed requiring a claims-centered cardiovascular outcomes study. DEPI completed their review of the Applicant's proposed synopsis in a review dated June 26, 2012. An overview of the required observational study was discussed with the Applicant at a teleconference on June 21, 2012 and

milestones were agreed to by the Applicant in a letter dated June 27, 2012, (received June 28, 2012).

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Comments:

- *I concur with the Medical Officer and CDTL's recommendation that a postmarketing required epidemiologic study be performed to further evaluate this potential safety finding of increased mean blood pressure, although the changes were clinically modest (ranging from a mean increase of 1-3 mm Hg).*
- *I also agree with the clinical review team that labeling reflect the available data on this signal of increased blood pressure and also include a warning for patients with severe uncontrolled hypertension not to use mirabegron.*

2. Potential risk of increased neoplasms:

In the long term extension study (178-CL-049), the clinical review team identified a difference between mirabegron and placebo in total number of neoplasm AEs when a variety of tumors, most reported by just one patient each, were added together. In the EU/Long-Term Study (Study 049), a higher incidence of SAEs reported as "neoplasms" was also observed in the mirabegron 100 mg group [11 subjects (1.3%)] compared to the mirabegron 50 mg group [1 subject (0.1%)] and the tolterodine group [5 subjects (0.5%)]. The reports included a wide variety of commonly occurring neoplasms, with no single neoplasm reported by more than 2 subjects.

A consult to the Division of Oncology Products 1 (DOP1) was sent to evaluate the imbalance in neoplasms that was observed in the long-term extension trial (Study 178-CL-049). The consult was completed on February 1, 2012 and had no additional recommendations with regard to the reported imbalance in Study 178-CL-049. The consultant review team agreed with the Applicant that the number of neoplasms reported was accurately reflected in the study report and suggested that the issue of whether further studies to evaluate the signal of neoplasm could be discussed at the April, 2012, Reproductive Health Advisory Committee meeting. In an addendum to the DOP1 consult (dated March 9, 2012), the team leader for DOP1 stated that they had reevaluated the original consult and tolterodine labeling and provided the following additional comment for the Division's consideration, "While a signal was not evident in the mirabegron 50 mg cohort, given the study size, the consultants cannot rule out an increased risk for the development and/ or detection of neoplasm."

At the April, 2012 Reproductive Health Advisory Committee (AC), the long-term study (178-CL-049) finding of a higher number of new malignant events in the mirabegron 100 mg group as compared to the mirabegron 50 mg group and tolterodine groups was discussed. The relative risk after the Applicant's adjudication for new malignant events was 1.5 (95% CI 0.5, 6.4) for total mirabegron versus tolterodine. Although several members of the AC expressed some concern about the increased reporting of adverse

events of neoplasms, the majority appeared to agree that some postmarketing evaluation of this finding of neoplastic events would be acceptable.

The Clinical Review team concurred with the Advisory Committee member's recommendation to perform additional postmarketing evaluation of this potential safety finding of increased reporting of neoplasms in the long term extension study and requested a consult from the Division of Epidemiology II.

The Division of Epidemiology was consulted to provide input on the design of the postmarketing required study to assess the incidence of new malignant events reported with mirabegron. DEPI and the Division met and discussed requiring a claims-centered study to capture the occurrence of new malignant events. DEPI completed their review of the Applicant's proposed synopsis in a review dated June 26, 2012. An overview of the required observational study was discussed with the Applicant at a teleconference on June 21, 2012 and milestones were agreed to by the Applicant in a letter dated June 27, 2012 (received June 28, 2012).

Comment: I concur with the Medical Officer and CDTL's recommendation that a postmarketing required study be performed to further evaluate this potential safety finding. In addition, I also agree with the clinical review team that labeling reflect the available data on this signal of neoplasms.

3. Potential for Glaucoma/Increased Ocular Pressure:

During drug development, 2 serious adverse events of glaucoma were identified. A series of extensive discussions occurred between the Applicant and the Division with input from a consultant from the Division of Transplant and Ophthalmologic Products regarding this potential signal. The Applicant subsequently conducted a systemic evaluation of glaucoma-type AEs in their safety database and also designed submitted Study 178-CL-081 to evaluate the effect of mirabegron on intraocular pressure (IOP).

Study 178-CL-081 was a randomized, double-masked, placebo-controlled, non-inferiority study designed to assess the effect of mirabegron 100 mg (supratherapeutic dose) administered orally once daily for 8 weeks on intraocular pressure (IOP) in healthy research subjects (N=160). Mirabegron was non-inferior to placebo for the primary endpoint of change from baseline to day 56 in subject-average IOP based on the non-inferiority limit of 1.5 mm Hg. IOP data from day 10 were concordant with day 56.

During evaluation of this signal of glaucoma, consultation was requested from the Division of Transplant and Ophthalmologic Products regarding evaluation of the potential glaucoma signal, design of Study 178-CL-081 and analysis of the final study report. In the consult, dated May 10, 2012, the supervisory Medical Officer stated that he agreed that, "Mirabegron in doses up to 100 mg daily does not appear to raise intraocular pressure" and that the consultant did not identify any other ocular safety issue and had no other recommendations regarding this potential safety issue.

In his Medical Officer review dated June 1, 2012, the Medical Officer concluded that, "This resolves this review issue."

Comment: I concur that the systematic review of the safety database and results of Study 178-CL-081 are sufficient to resolve this potential safety issue and no further studies or data are necessary.

4. Delayed hypersensitivity reactions:

During the mirabegron clinical development program, 2 events with findings suggestive of drug hypersensitivity reaction were reported in 2 subjects (investigator-reported as preferred terms [PTs] of Stevens-Johnson syndrome [SJS] in [Patient No. 178-CL-045, P00244] and leukocytoclastic vasculitis in [Volunteer No. 178-CL-076, U00022981217]). These two reports prompted the Applicant to perform additional evaluations of possible hypersensitivity reactions in the safety database as part of the NDA submission.

The Applicant had an Expert Committee review the subject data for 257 subjects from the global database (2.6%) with 290 potential hypersensitivity events. Of these potential events, 44 subjects were categorized as having plausible hypersensitivity including two cases of leukoclastic vasculitis where mirabegron could not be excluded as a potential cause. No patients developed anaphylaxis or angioneurotic edema. The issue of these delayed hypersensitivity reports was also discussed as a topic at the April 5, 2012, Advisory Committee.

In his June, 2012, review, the Medical Officer concluded that, "Lacking a clear alternative, and given a positive de-challenge, a causal association with mirabegron cannot be ruled out. Consideration should be given to include this adverse event in labeling."

Comment: Although there were some members of the Advisory Committee who expressed concerns regarding the delayed hypersensitivity reactions, after review of the limited data from the available reports, I concur with the clinical review team that the rare reports of these serious episodes of leukoclastic vasculitis should be included in labeling. Leukoclastic vasculitis is included as an adverse event in the Clinical Trials Experience section of final labeling for mirabegron.

5. Postmarketing data summary:

Mirabegron was approved for marketing in Japan (tradename – Betanis) in July, 2011 at the 25 mg and 50 mg doses. As of February, 2011, a limited number (37) of reported cases received by the Applicant were reviewed by the Medical Officer. From these reports, of particular interest to the clinical review team were 18 reports of urinary retention, some requiring catheterization.

After review of these reports of urinary retention, the Medical Officer stated that, "It would be reasonable to have a Postmarketing section in labeling and to include some of

the reported events (e.g. urinary retention). The episodes of urinary retention in some patients, especially those taking anti-muscarinics and in men with BPH (benign prostatic hypertrophy), are notable.

Comment: The postmarketing reports from Japan of urinary retention were included in the Postmarketing section of final labeling for mirabegron.

Safety summary:

The safety database for Myrbetriq (mirabegron) tablets has been determined by the review teams to be sufficient and supports approval for patients with overactive bladder. The safety data provided adequate patient exposure and supported use of both proposed doses, 25 mg and 50 mg. The clinical review team, the Applicant and CDER consultants as well as the Reproductive Health Advisory Committee members have analyzed adverse events through evaluations of the pivotal phase 3 database, the extension study database and the global databases. The majority of the safety issues identified were addressed in labeling including reports of hypersensitivity and urinary tract adverse events. To address the specific safety concern of reports of hepatic adverse events, collection and review of these events will be evaluated through enhanced pharmacovigilance by the Applicant and submitted as a separate report addendum to the required periodic adverse event reports (PADERs).

The clinical review team, however, determined that there were two outstanding safety issues identified that were not sufficiently addressed after review of the NDA safety database. These remaining safety issues included: 1) the potential effects of the mean increases in blood pressure and heart rate on cardiovascular outcomes and 2) the increased reports of a variety of neoplasms in the 100 mg dose group in the long-term extension study (178-CL-049). The clinical team agreed that these safety issues could be further evaluated through two postmarketing requirements. The Division of Epidemiology reviewed the proposed protocol synopses for the postmarketing requirements and determined that the synopses were acceptable.

In summary, the Medical Officer concluded the following on the safety database for mirabegron in his review dated June 1, 2012: "The studies performed by the Sponsor for the treatment of overactive bladder (OAB) are adequate to assess the safety of mirabegron used once a day for the treatment of OAB. The results largely demonstrate that mirabegron is generally well-tolerated in the treatment of OAB."

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's recommendation that the safety profile of mirabegron was acceptable in his CDTL review (dated June 26, 2012) and stated, "Overall, then, there are no unresolved efficacy or safety issues for this application and the risk/benefit ratio is considered acceptable for marketing approval."

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA. The clinical review

team also determined that two identified safety issues (potential increase in cardiovascular outcomes and increased reporting of neoplasms) could be evaluated as postmarketing requirements. I concur that these issues need to be further assessed through postmarketing requirements. Additional details on these postmarketing requirements are briefly outlined in section 12 below.

9. Advisory Committee Meeting

On April 5, 2012 a Reproductive Health Drugs Advisory Committee meeting was held to discuss the efficacy and safety data for mirabegron as a new molecular entity. The focus of the discussion included the efficacy of the product, the blood pressure findings from phase 1 and 3 studies, the increased reports of neoplasms at the 100 mg dose, identified hepatic adverse events and hypersensitivity reactions. A summary of the Committee voting on the following three questions is outlined below:

1. Do the data provide substantial evidence of benefit for mirabegron in the treatment of overactive bladder? (**VOTING QUESTION**)

Committee voted Yes 8, No 4 and Abstain 0

2. Has adequate safety been demonstrated for mirabegron in the treatment of overactive bladder? (**VOTING QUESTION**)

Committee voted Yes 9, No 3 and Abstain 0

3. Considering all the available data, including information from the briefing documents and today's discussion, does the overall benefit-risk assessment support approval of mirabegron for the treatment of overactive bladder? (**VOTING QUESTION**)

Committee voted Yes 7, No 4, Abstain 1

After each question, each Committee member was asked for the rationale for his or her vote. In terms of efficacy, all agreed with the Applicant that the clinical endpoints had been met, although some questioned the clinical benefit. In terms of safety, the starting dose and concerns regarding the cardiovascular, hepatic, hypersensitivity and cancer risks were raised by several committee members. In addition, several committee members recommended postmarketing "monitoring" and studies to evaluate the reported safety signals. In summary, the majority of the members appeared to feel that there was adequate information to allow approval of mirabegron.

Comment: I generally concur with the guidance and recommendations provided by the Reproductive Health Drugs Advisory Committee. The majority of the recommendations regarding efficacy and dosing were incorporated into labeling. The safety concerns raised by the committee regarding cardiovascular outcomes and reports of neoplasms will be further evaluated through postmarketing required studies.

10. Pediatrics

The Sponsor requested a partial waiver of pediatric studies in patients from birth through 4 years and a deferral in patients 5-17 years. The Division presented to the PeRC subcommittee on May 30, 2012. The Division presented a partial waiver for patients at birth through 4 years because studies are impossible or highly impracticable because overactive bladder is not a condition in infants or young children and a deferral in patients 5-17 years until additional safety or efficacy data have been collected. The waiver was requested because overactive bladder is not a condition in infants or young children 0 to 4 years and 11 months who are not yet bladder trained.

In addition, there were nonclinical and clinical reasons for deferring studies in pediatric patients older than 5 years. First, appropriate animal studies have not yet been performed. An area of nonclinical concern is a potential effect on bone maturation. Second, the main clinical areas of concern are the effect of mirabegron on increasing blood pressure and a potential effect on new malignant events in adult. Both these clinical concerns will be addressed in required postmarketing adult studies to inform future pediatric studies.

The PeRC agreed with the Division to grant a partial waiver in patients (from) birth through 4 years, and to the deferral in patients 5 through 17 years of age.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) on June 8, 2012, and found it to be acceptable with several recommended changes. The Division discussed several of the recommendations with DMPP, and after minor editing, the agreed to recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information and the Patient Package Insert. OPDP completed their review of Prescribing Information on June 13, 2012. The Division discussed several of the recommendations with OPDP, and after editing, the agreed to recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI conducted inspections of three clinical sites (Drs. Koltun, Goldfischer and Hoye) and the Applicant (Astellas Pharma US, Inc.) in support of this NDA. After these inspections were conducted and assessed by OSI, the Clinical Inspection Summary stated that, "Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication." (See OSI Clinical Inspection Summary dated May 8, 2012)

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team provided a final review on May 31, 2012, of carton and container labels for areas of vulnerability that could lead to medication errors. DMEPA's recommendations were implemented.

DMEPA also assessed the proposed tradename "Myrbetriq" on June 12, 2012, and found it acceptable.

Financial Disclosures**:**

The clinical review team did not identify any issues related to financial disclosures for the phase 3 studies (See clinical review dated June 1, 2012).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team reviewed the label in a review dated June 27, 2012, and provided recommendations. These recommendations were implemented.

12. Labeling

Labeling discussions are complete. Labeling for Myrbetriq (mirabegron) was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was reviewed by the Study Endpoints and Label Development (SEALD) Team. An edited version of the label was sent to the Applicant. The Applicant accepted the requested edits from SEALD. No additional labeling review by SEALD was required.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that the Myrbetriq (mirabegron) tablet application should receive an Approval action.

Risk Benefit Assessment:

Efficacy and safety data from the three pivotal adequately controlled trials (178-CL-046, 178-CL-047 and 178-CL-074) using accepted endpoints have demonstrated that mirabegron tablets were effective in the treatment of overactive bladder at the 25 mg and 50 mg doses. The results from these three trials were consistently statistically significant, and efficacy has been demonstrated in the population of patients with overactive bladder.

No safety concerns were identified in clinical trials with mirabegron tablets that precluded approval. The safety database was sufficient at the proposed doses of 25 mg and 50 mg for evaluation and included 3 pivotal trials (178-CL-046, 178-CL-047 and 178-CL-074) and an extension study (178-CL-049) that provided adequate patient exposure. Several specific safety concerns were identified during the mirabegron clinical review including:

- Modest increases in blood pressure and heart rate during the Phase 3 studies
- Increase in reported events of neoplasms at the 100 mg dose group compared to the 50 mg dose group and tolterodine active-control group
- Reports of hepatic adverse events

The reported increases in blood pressure and neoplasms identified in the pivotal clinical trials will be further evaluated through two postmarketing requirements. The Applicant has also agreed to provide enhanced pharmacovigilance of the reports of hepatic adverse events as an addendum to their postmarketing periodic adverse event reports (PADERs).

In my opinion, the risk/benefit assessment favors approval of Myrbetriq (mirabegron) for the treatment of overactive bladder.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for this product.
- The Division and the Division of Epidemiology II review teams recommended the following two postmarketing requirements (PMRs):
    - A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron).

- A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron).

The Applicant proposed acceptable milestones for completion of these trials.

Comment: At the June 21, 2012 teleconference to discuss an overview of the PMRs, the Applicant was informed that if the proposed epidemiologic studies were not successful, an interview (or survey) -based, prospective cohort study of the safety signal would follow. Further discussion with the Applicant regarding the proposed milestones was also conveyed at a teleconference on June 26, 2012. The final agreed-to milestones were agreed to by the Applicant in a letter dated June 27, 2012 (received June 28, 2012).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
06/28/2012