

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202611Orig1s000

Trade Name: Mybetriq

Generic Name: mirabregon

Sponsor: Astellas Pharma

Approval Date: June 28, 2012

Indications: For the treatment of overactive bladder

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 202611

NDA APPROVAL

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Dr. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myrbetriq (mirabegron), 25 mg and 50 mg extended release tablets.

We acknowledge your amendments received September 12, October 11, 13, and 20, November 8 and 29, December 2, 8 (2), 9, 14, 16, 22, and 23, 2011; January 17, February 8, 9 (2) and 21, March 7 (2), 20, and 23, April 3, 11, 12, 17 and 18, May 4 (2), 9, 11(2), 16, 18, June 1, 5, 25, and 28 (2), 2012.

This new drug application provides for the use of Myrbetriq (mirabegron), 25 mg and 50 mg, for the treatment of overactive bladder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your May 18, 2012, submission containing final printed carton and container labels.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202611.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years and 11 months because overactive bladder is not a condition in infants or young children who are not yet bladder trained and, therefore, necessary studies are not possible or highly impracticable.

We are deferring submission of your pediatric studies for ages 5 to 17 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

1898-1 Open label, multicenter single ascending dose study to evaluate pharmacokinetics, safety and tolerability of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with neurogenic detrusor overactivity (NDO) or overactive bladder (OAB).

Final Protocol Submission:	January 2016
Study Completion:	September 2017
Final Report Submission:	September 2018

1898-2 Open label, baseline-controlled, multicenter, sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, safety and efficacy of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with NDO.

Final Protocol Submission:	January 2018
Study Completion:	June 2023
Final Report Submission:	June 2024

Submit the protocols to your IND 069416, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risk related to: 1) observed increases in mean systolic and diastolic blood pressure and 2) increased reporting of new malignant events in the long-term clinical trial of Myrbetriq (mirabegron) at the 100 mg dose.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1898-3 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).

The timetable you submitted on June 27, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Assessment and Summary Report Submission:	March 2015
Interim Study Completion:	June 2017
Interim Analysis Report:	June 2018
Final Study Completion:	July 2018
Final Report Submission:	June 2019

1898-4 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 timetable you submitted on June 27, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Assessment and Summary Report Submission:	March 2015
Interim Study Completion:	June 2017
Interim Analysis Report:	June 2018
Final Study Completion:	July 2018
Final Report Submission:	June 2019

Submit the protocols to your IND 069416, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also request that you submit with your periodic adverse event reports an additional summary of postmarketing hepatic adverse reports for a period of 3 years following launch of Myrbetriq in the US.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Victoria Kusiak, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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

/s/

VICTORIA KUSIAK
06/28/2012