CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022225Orig1s000

Trade Name:	BRIDION Injection, 100 mg/mL.
Generic Name:	Sugammadex
Sponsor:	Organon USA Inc., a subsidiary of Merck & Co., Inc..
Approval Date:	December 15, 2015
Indication:	For the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	**X**
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022225

NDA APPROVAL

Organon USA Inc., a subsidiary of Merck & Co., Inc.
126 East Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Attention: Dori L. Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your New Drug Application (NDA) dated October 30, 2007, received October 31, 2007, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRIDION (sugammadex) Injection, 100 mg/mL.

We acknowledge receipt of your amendment dated June 19, 2015, which constituted a complete response to our April 22, 2015, action letter.

This new drug application provides for the use of BRIDION (sugammadex) Injection, for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.

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. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available 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

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels 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 *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 022225**." Approval of this submission by FDA is not required before the labeling is used.

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

EXPIRATION DATING PERIOD

An expiry of 36 months for the drug product when stored at 25°C is granted.

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 deferring submission of your pediatric final study report until September 2021, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

3003-1 A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old.

Final Protocol Submission:	January 2017
Trial Completion:	May 2021
Final Report Submission:	September 2021

Submit the protocol to your IND 068029, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study 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 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.

In the clinical trials conducted as part of the development program for sugammadex injection, some patients experienced bradycardia and other cardiac arrhythmias, with some cases resulting in cardiac arrest.

Also, in the clinical trials, some patients had either a delayed response or no response to sugammadex injection. These “non-responders,” may be at risk for the following adverse consequences:

a) The administration of additional doses of sugammadex that could place them at higher risk for hypersensitivity reactions and/or anaphylaxis;
b) The need for continued ventilator support and sedation which carry their own potential for additional adverse consequences;
c) The risk of anoxia if they had received high doses of neuromuscular blocker because of expectations that sugammadex would be able to immediately reverse the neuromuscular blockade.

Thus, being able to identify potential non-responders to treatment with BRIDION (sugammadex) would contribute to safer use of the drug.

Additionally, because morbidly obese subjects were not well represented in the development program and sugammadex administration is based on actual body weight, morbid obesity may result in higher than necessary doses being given.

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 the known serious risks of:

- cardiac arrhythmias in a population of American Society of Anesthesiologists Class 3 and 4 patients;
- anaphylaxis or hypersensitivity syndrome with sugammadex in patients not responding to the drug;
- anaphylaxis or hypersensitivity syndrome with sugammadex in morbidly obese patients

- prolonged ventilatory support and anoxia in patients not responding to sugammadex.

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 these serious risks.

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

3003-2 Conduct a postmarketing study to analyze the demographic characteristics, concomitant medication use, and comorbid conditions in patients who did not respond to sugammadex reversal in the development program, in postmarket studies that have been conducted, or as described in cases of non-response/lack of efficacy reported as postmarketing adverse events. The goal of the study is to determine the characteristics and profile of patients who would be expected to be non-responders. The study should also assess the occurrence of hypersensitivity or anaphylaxis, prolonged ventilator support and sedation, and anoxia in these patients.

The timetable you submitted on December 9, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2016
Study Completion:	January 2017
Final Report Submission:	May 2017

Finally, we have determined that clinical trials (rather than a nonclinical or observational study) will also be necessary to assess a known serious risk of bradycardia or other cardiac arrhythmias, and anaphylaxis or hypersensitivity syndrome with sugammadex.

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

3003-3 Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in a population of American Society of Anesthesiologists Class 3 and 4 patients. The goal of the trial is characterization of the risks of bradycardia and other cardiac arrhythmias after sugammadex administration in this population that may have more severe outcomes related to cardiac arrhythmias experienced during reversal of neuromuscular blockade. Prespecify the case definition of bradycardia, tachycardia, and the other cardiac arrhythmias of interest.

The timetable you submitted on December 9, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2017
Trial Completion:	March 2020
Final Report Submission:	August 2020

3003-4 Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in patients with morbid obesity. The goal of the trial is to evaluate the safety of sugammadex (including the serious adverse outcomes of anaphylaxis or hypersensitivity) and to generate data to support dosing recommendations in morbidly obese patients, specifically whether to dose by actual vs. ideal body weight. Prespecify the case definition of morbid obesity that will establish who will be included in the trial.

The timetable you submitted on December 9, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2017
Trial Completion:	October 2018
Final Report Submission:	March 2019

Submit the protocol(s) to your IND 068029, with a cross-reference letter to this NDA.

Submit all final report(s) 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, Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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).

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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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, call Diana L. Walker, Ph.D., Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
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/

CURTIS J ROSEBRAUGH
12/15/2015