



NDA 022225/S-006

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT**

Organon USA Inc.; a subsidiary of Merck & Co., Inc.
26 E. Lincoln Avenue,
P.O. Box 2000, RY34-B188
Rahway, NJ 07065

Attention: Dori Glassner
Director, Global Regulatory Affairs

Dear Ms. Glassner:

Please refer to your supplemental new drug application (sNDA) dated and received, August 9, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bridion (sugammadex) Injection.

This Prior Approval supplemental new drug application proposes revisions to the **USE IN SPECIFIC POPULATIONS** section of the package insert to include the results of Study P146, entitled, *A Phase 4 Randomized, Active-Comparator Controlled Trial to Study the Efficacy and Safety of Sugammadex (MK-8616) for the Reversal of Neuromuscular Blockade Induced by Either Rocuronium Bromide or Vecuronium Bromide in Morbidly Obese Subjects*, to fulfill the requirements of PMR 3003-4.

APPROVAL & LABELING

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.

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 FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated August 9, 2019, containing the final report for the following postmarketing requirement listed in the December 15, 2015, approval letter.

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.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the July 11, 2018, postapproval postmarketing requirement letter that are still open.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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.

Since Bridion was approved on December 15, 2015, we have become aware of a potential increase in risk of adverse events, specifically related to the effects of bradycardia, in pediatric patients with obesity. The sNDA dated August 9, 2019, included results of Study 146-01, which evaluated the pharmacokinetics, safety, and efficacy in adult patients who were morbidly obese. The results of the study demonstrated that plasma levels of sugammadex for patients dosed using actual body weight (ABW) was higher compared to patients dosed using ideal body weight (IBW). While ABW dosing did not result in increased incidence of adverse events, it is not clear whether this finding would be applicable to the pediatric population. The higher plasma levels may result in a higher incidence of bradycardia, and pediatric patients are at higher risk of the adverse events related to bradycardia. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

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 risk of bradycardia or other dose-related adverse events in pediatric patients with obesity.

Furthermore, the active postmarket risk identification and analysis system as available 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:

- 3003-10 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 pediatric patients ages 2 years to less than 17 years with obesity, defined as body mass index (BMI) at or above the 95th percentile for age and gender. The goal of the trial is to evaluate the pharmacokinetics, safety, and efficacy of sugammadex and to generate

data to support dosing recommendations in pediatric patients with obesity, specifically whether to dose by actual vs. ideal body weight.

The timetable you submitted on June 8, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/ 2021
Final Protocol Submission:	11/ 2021
Trial Completion:	11/ 2024
Final Report Submission:	06/ 2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 068029, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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.

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

REPORTING REQUIREMENTS

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

If you have any questions, call Allison Meyer, Senior Regulatory Health Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine,
and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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