

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022225Orig1s000

OTHER ACTION LETTERS



NDA 022225

COMPLETE RESPONSE

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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sugammadex Injection, 100 mg/mL.

We acknowledge receipt of your amendments dated October 22 and 23, and December 9, 2014, and January 20 and 30, February 12 and 24, and March 3, 6, 10, and 11, 2015.

The October 22, 2014, submission constituted a complete response to our September 20, 2013, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

The audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P101.

Information Required to Address Deficiency:

1. For Study P101, identify all subjects with a major protocol violation, including those for whom the investigators did not follow the protocol regarding the administration of the study drug and assessments of hypersensitivity and anaphylactic reactions. Evaluate whether there is a difference in the nature, frequency, and severity of the signs and symptoms of hypersensitivity and anaphylaxis between the violation group and the per protocol groups for each of the treatments. Perform sensitivity analyses on the primary and key secondary endpoints with the data from the per protocol subjects.

- a) Identify the subjects whose data were unblinded to the statisticians (those enrolled before April 8, 2014) and perform a sensitivity analysis comparing the findings to those treatment-blinded subjects (subjects enrolled after April 8, 2014 when the identifying variable in the dataset was deleted). Also, include an evaluation of the incidence rate and types of adverse events.
- b) Perform a sensitivity analysis comparing the study findings prior to and after the unblinding and also when blinding was re-established. Include an evaluation of the incidence rate and types of adverse events for the following time intervals:
 - Time Interval 1: Prior to March 11, 2014 (data given to company statistician-possible unblinding)
 - Time Interval 2: Between March 11, 2014 and April 8, 2014 (unblinded period)
 - Time Interval 3: After April 8, 2014 (blinding possibly re-established)
- c) For all sensitivity analyses (protocol violation and unblinding), provide a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the study findings, thereby allowing the study to address the deficiency cited above. Submit the source documents utilized to support the inclusion of the remaining subjects incorporated in the reanalyses.

OR

2. Repeat Study P101 and submit the clinical study report to the Agency.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

PROPRIETARY NAME

Please refer to correspondence dated December 23, 2014, which addresses the proposed proprietary name, Bridion. This name was found acceptable pending approval of the application

in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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/s/

CURTIS J ROSEBRAUGH
04/22/2015



NDA 022225

COMPLETE RESPONSE

Organon USA, Inc.
P.O. Box 2000, RY33-204
Rahway, NJ 07065

Attention: Dori L. Glassner
Director, Worldwide Regulatory Affairs

Dear Ms. Glassner:

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

We acknowledge receipt of your amendments dated December 19, and 21, 2012, and January 14 (2) and 23, February 7, 13, 18, 19, 21, 22, 26 and 27, March 1, 4 and 26, April 12, 17 and 19, May 6, 8, 10, 23, 24 and 31, June 21, 25, and 27, July 10 and 15, August 1, 14 and 28, and September 13, 2013.

The December 19, 2012, submission constituted a complete response to our July 31, 2008, action letter.

We also acknowledge receipt of your amendment dated September 11, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

During the first review cycle of this NDA, one of the conclusions was that the sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug and the time course for events (potential for delayed reactions). Study P06042 was designed and conducted to address this deficiency. The audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P06042 such that this deficiency remains unresolved.

Information Required to Address Deficiency:

1. For Study P06042, identify all subjects with a major protocol violation, including those for whom treatment and adverse event evaluations could potentially be unblinded by the investigators and those whose data were potentially compromised because the site used an inadequate case report form that did not capture all adverse event data elements. Perform sensitivity analyses on the primary and key secondary endpoints with the data from the remaining subjects. Provide a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the findings, thereby allowing the study to address the deficiency cited above. Submit the source documents utilized to support the inclusion of the remaining subjects incorporated in the reanalyses.

OR

2. Repeat or conduct a trial similar to Study P06042 and submit the clinical study report to the Agency. If you choose to pursue this pathway, please discuss the trial protocol with the Agency prior to initiation.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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/s/

CURTIS J ROSEBRAUGH
09/20/2013



NDA 22-225

NDA NOT APPROVABLE

Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: June Bray
Vice President, Regulatory Affairs

Dear Ms. Bray:

Please refer to your new drug application (NDA) dated October 30, 2007, received October 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for sugammadex sodium.

We acknowledge receipt of your submissions dated November 19, 20, and 27, and December 13(2), 2007, and January 14, 16, 21, 22, 24, 30, and 31, February 1, 6, 15, 19, 25, 26, and 27(2), March 3, 10, 14, 19, and 25, April 10 and 17, May 15, 16, and 21, June 4, 9, 10, and 13, and July 7, 2008.

We also acknowledge receipt of your submission dated June 27, 2008. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

CLINICAL

1. The sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug. Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure. As widespread use of sugammadex sodium is expected, an individual patient may be exposed to the drug multiple times. This expected pattern of use is of concern because the risk of Type I hypersensitivity, including anaphylaxis, is likely to increase on repeat exposure.

2. The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program. The in vitro assessment indicated that sugammadex increased activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and the International Normalized Ratio (INR). In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol-specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined. The mechanism and the clinical significance of the effects of sugammadex on coagulation are not known.

Information Required to Address Deficiencies:

1. Characterization of the safety of sugammadex sodium on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. Exposure of subjects to repeat doses of sugammadex sodium should occur at time intervals sufficient to permit formation of drug-specific IgE, such as at least a minimum of 5 to 6 weeks. Define the frequency, time course of events related to sugammadex sodium administration, and other characteristics of the adverse reactions. Attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium. The clinical program will inform the safety risk of sugammadex sodium on repeat exposure. Development of a predictive test will be useful in predicting risk and potentially in avoiding exposures to patients at risk for an anaphylactic reaction.
2. Studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Anesthesia, Analgesia, and Rheumatology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

ADDITIONAL COMMENTS AND REQUESTS

While not approvability issues, we have the following comments/suggestions/requests for additional information:

Pediatrics

Nonclinical evaluations will be necessary prior to any multiple-dose pediatric trials, approval of a pediatric indication, or inclusion of pediatric data in the label:

1. Provide an evaluation of sugammadex in a nonclinical model of bone fracture to examine potential effects of the drug on bone healing. You are encouraged to submit protocols of such studies to the Agency for comment prior to their conduct.
2. Provide data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study.
3. Provide a repeat-dose study of sugammadex in the juvenile rat with an extended period of recovery, such that bone length, material properties, and integrity at full skeletal maturity may be evaluated in order to clarify the observation of slight but lasting decreased bone length and body weight observed in the 28-day juvenile toxicity study. Within this study, micro-computed tomography (μ CT), bone turnover markers, and bone strength assessment should be obtained and evaluated. Also, the study should incorporate positive control arms to verify assay sensitivity. Lastly, though not required, the inclusion of vertebral evaluation would be helpful to interpret bone effects since vertebrae have a more homogenous trabecular structure than long bones such as femur. You are encouraged to consider an alternative, intermittent dosing paradigm in order to minimize effects of sugammadex on body weight while allowing for significant drug accumulation in the skeleton.
4. Provide definitive information on the binding site of sugammadex in bone as well as a reevaluation of bone localization of sugammadex as presentation of the data on bone localization was not clear and errors in descriptions were noted in the submitted materials.
5. Provide data, which may be derived from published literature, in vitro studies, and/or in vivo studies, along with a persuasive, well-supported rationale, to show that the risk of administration and long-term retention of sugammadex in the bones of pediatric patients will not confer a risk for bone tumor development in this population. Otherwise, an evaluation of the carcinogenic potential of sugammadex may be required. Although plasma levels of sugammadex rapidly decline with acute administration, the long retention of sugammadex in skeletal bone may be considered to be chronic exposure (i.e., greater than six months) and raises concern regarding the potential for development of tumors of this tissue, especially in the pediatric population, which is known to develop primary bone tumors at rates that exceed those in the adult population.

Other Studies

Although not required for approval, the following studies are recommended:

1. Additional studies to address the potential local effects in bone, such as in vitro bone resorption assay (^{45}Ca release), assessment of bone turnover markers, hydroxyl apatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention.
2. A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.
3. A study to assess clearance of sugammadex-rocuronium complexes in patients with renal failure who undergo hemodialysis using high flux filtration.
4. Studies to assess safety, efficacy, and dosing requirements for sugammadex when used in patients with hepatic impairment. The studies should characterize the pharmacokinetics and pharmacodynamics of rocuronium and vecuronium in these patients following the administration of sugammadex.
5. Studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. Such studies should not be started until the safety issues for the adult population have been fully vetted by the Agency.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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