

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022225Orig1s000**

**OFFICE DIRECTOR MEMO**

## Summary Basis for Regulatory Action

<b>Date</b>	December 15, 2015
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	22-225
<b>Supp #</b>	
<b>Applicant</b>	Merck/Organon USA
<b>Proprietary / Established (USAN) Names</b>	Bridion Sugammadex Sodium
<b>Dosage Forms / Strength</b>	Sterile solution, injectable 100 mg/mL
<b>Proposed Indication(s)</b>	1. Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium 2. Immediate reversal of NMB at 3 minutes after administration of rocuronium
<b>Action:</b>	<i>Approval</i>

### 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding sugammadex, and I refer the reader to the reviews in the action package for a more detailed discussion. This is a review (4<sup>th</sup> cycle) of the Complete Response (CR) to the Complete Response Action that was taken on April 22, 2015. The CR action requested evaluation by various sensitivity analyses to determine whether protocol deviations regarding Study P101 (unblinding of data) could impact the validity, reliability, and integrity of the data. The sponsor performed the requested evaluations and submitted them with this response.

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex was designed so that the negatively charged sugar groups within its center would attract the positively charged ammonium groups of rocuronium bromide (RCB) and vecuronium bromide (VCB) and sequester these neuromuscular blocking agents within its core by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of RCB and VCB within sugammadex renders them inactive and thereby reverses paralysis that otherwise would have occurred due to their activity at the neuromuscular junction.

This application was not approved on the first cycle due to safety concerns observed during clinical development related to hypersensitivity/anaphylaxis reactions (no information on mechanism and repeat exposure) and the effects of the product on coagulation and bleeding. During the first cycle review, this application was granted a priority review and was presented at a meeting of the Anesthesia and Life Support Drugs Advisory Committee (ALSDAC)<sup>1</sup> on

March 11, 2008. The anaphylaxis concern was noted late in the review, just before the advisory committee (AC) meeting, and did not benefit from a full analysis prior to the AC meeting. Therefore, committee members (mainly anesthesiologists or pain experts) had minimal information regarding the anaphylactic potential of sugammadex<sup>2</sup> to use in safety considerations when advising about marketability. While the Committee voted for approval they did not have access to all the relevant safety information and allergy expertise was not available to enrich the discussion regarding conclusions and marketability. Therefore, a Not Approvable action was taken for the first review cycle.

The information included in the CR that led to the CR action on September 20, 2013, included several new studies and trials, the most relevant being Trial P06042. This trial was a repeat administration of the mid (4 mg/kg) and high dose (16 mg/kg) of sugammadex designed to be conducted in a blinded fashion to obtain further information on anaphylaxis with sugammadex use regarding the incidence, time course and risks associated with re-exposure. However, during the course of inspection of site #2 the Office of Scientific Investigation (OSI) investigators found that there had been unblinding, calling into question the integrity of the data from that site (see details from my review of September 20, 2013). After further investigation, the applicant notified us that there were protocol violations at the remaining three sites as well where study staff administered the study medication and also performed the safety evaluations. This called into question data integrity from all the sites where the study was conducting leading to cancellation of a planned AC meeting and subsequent CR action.

With the next submission, the sponsor had conducted Trial P101 which is a repeat dose trial similar to Trial P06042. However, an OSI inspection identified possible data integrity issues from this trial as well. The first issue was with data management at Merck. The statistical staff at Merck, upon extracting SAS data sets from the Clinical Data Repository (CDR), noted that one column was not properly blinded. This could lead to full un-blinding of the trial. Access and realization of un-blinding potential occurred in early March of 2014, when all randomized subjects had received at least one dose of assigned treatment, but before anyone had received a third dose. Merck stated that 11 people had access to these data and that they took action to correct this problem and received signed attestations from all employees involved that they did not contact study sites or unblinded investigators to treatment. However the 11 people that had access had been terminated from employment at Merck by the time of our inspection and were not available for interview. Merck deleted all records of the unblinded data from the local server and individual computers and the data system they used did not have an audit trail to inspect.

A second issue noted was that when OSI inspected two of the six study sites, one had a protocol violation where the assessor of adverse events was also giving dosing. This occurred in the first six subjects. The protocol requires different people administer the drug and do the adverse event assessments. While the person administering the drug did not do the assessment in the same subject, this was a major protocol violation, the same issue that made the first trial

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<sup>1</sup> The ALSDAC has since been renamed the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC).

<sup>2</sup> There was not any repeat-dose data available.

invalid, and raised concerns about what may have happened at the four sites that have not been inspected.

This submission, which is intended to respond to last CR, included various sensitivity analyses exploring whether the trial results varied before compared to after the time point of central unblinding. Also, since the last action all sites have been inspected by the Office of Scientific Investigations (OSI). OSI did not find protocol violations that would preclude use of data from any of the remaining sites. Also, no analyses demonstrated concerning findings that trial conduct varied at any point. Therefore, the Agency considered the data secure and the results were presented at an Advisory Committee meeting. Additional, since the time of the first CR action, sugammadex has been approved in many markets outside of the United States, and post-marketing adverse event data has become available from those countries for examination.

Results of study P101 demonstrated a frequency of 0.33% (1/299) and the entire original application revealed an anaphylaxis rates of 0.1%-0.3% (1.4% was demonstration in a population of healthy subjects). Study P101 demonstrated that repeat exposures to sugammadex did not increase hypersensitivity/anaphylaxis rates. Also, the extensive post-marketing adverse event reporting data available for review has not revealed a concerning excess of anaphylaxis events. Mechanistic studies are not suggestive of IgE-mediated mechanism although the underlying mechanism cannot be determined.

## **2. Advisory Committee Meeting**

A meeting of the Anesthetic and Analgesic Drug Products Advisory Committee was held on November 6, 2015. Voting to the question regarding whether the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of this application resulted in 14 yes votes, with 0 no or abstain votes.

## **3. Conclusions and Recommendations**

Evaluation has led to the conclusion that none of the sites for P101 have major protocol violations and that we can rely upon the data from for regulatory purposes. Sensitivity analyses demonstrated that there was not systematic un-blinding related to the central event. Therefore, the results of Trial P101 were presented to an advisory committee meeting. At this time, the team is recommending approval of sugammadex with appropriate labeling and PMR studies. The general consensus is that a neuromuscular blocker reversal agent that can quickly reverse blockade with minimal consequence would be beneficial to public health. I agree with their assessment.

I recommend an approval action with appropriate labeling.

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/s/  
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CURTIS J ROSEBRAUGH  
12/15/2015

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