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APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management Review

Application Type NDA

Application Number 22225

OSE RCM # 2015-706

Reviewer Name(s) Leah M. Hart, PharmD

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Review Completion Date November 27, 2015

Established Name Sugammadex

(Proposed) Trade Name Bridion

Applicant Organon USA Inc.

Therapeutic Class Neuromuscular blockade reversal agent

Formulation(s) 100 mg/mL concentration, Injection

Dosing Regimen 2mg/kg – 16mg/kg administered as a single bolus injection

Proposed Indication(s) Reversal of the effects of rocuronium bromide and vecuronium bromide (b) (4) surgery in adults

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EXECUTIVE SUMMARY

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Bridion (sugammadex), NDA 22225, submitted initially by Organon USA Inc. (Organon) on October 30, 2007. The NDA received three Complete Responses (CR); Merck, Sharp & Dohme Corp. (Subsidiary of Merck & Co., Inc., on behalf of Organon USA Inc., which is also a subsidiary of Merck & Co., Inc.) submitted sugammadex for a fourth-cycle review on June 19, 2015. A REMS was not submitted by the applicant.

No new Applicant-initiated studies were contained in this submission; however the safety database was updated. The safety concerns of interest are cardiac dysrhythmias, and anaphylaxis; both of which were discussed at a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on November 6, 2015.

Based upon the review of the clinical data and the discussion by the AADPAC, DRISK and the Division of the Division of Anesthesia, Analgesia, and Anesthetic Products (DAAAP) have determined that a REMS is not necessary to ensure that the risk of cardiac dysrhythmias and anaphylaxis outweigh the benefits of the sugammadex. The prescribers/administrators of sugammadex will likely be specialists, specifically anesthesiologists or certified registered nurse anesthetists (CRNA), both of which are trained to monitor and treat intraoperative complications including cardiac dysrhythmias and anaphylaxis. Both of these safety issues will be included as warnings in the final approved labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) sugammadex is necessary to ensure the benefits of this product outweigh its risks. Merck, Sharp & Dohme Corp. (Merck) submitted a New Drug Application (NDA 22225) for sugammadex with the proposed indication of reversal of the effects of rocuronium bromide and vecuronium bromide (b) (4) in adults. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Sugammadex is a new molecular entity (NME), a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex is designed with a negatively charged core that specifically attracts the positively charged ammonium groups of rocuronium bromide (rocuronium) and vecuronium bromide (vecuronium). Sugammadex sequesters these neuromuscular blocking agents (NMBA), rendering them unavailable to bind to nicotinic receptors

at the neuromuscular junction, resulting in reversal of the neuromuscular blockade. Sugammadex is available as 200mg and 500mg single dose vials for administration by intravenous route.

The proposed indication is for the reversal of the effects of rocuronium bromide or vecuronium bromide (b) (4) in adults. This would be the first product-specific reversal agent approved for this indication. Sugammadex will be given in an intraoperative setting as an intravenous (IV) bolus injection given over 10 minutes to patients who have been paralyzed with either rocuronium or vecuronium and are sedated.

The proposed dose regimen is:

For reversal of rocuronium and vecuronium:

4 mg/kg is recommended if recovery of the twitch response has reached 1-2 post-tetanic counts (PTC) and there are no twitch responses to a train-of-four (TOF) stimulation. (2.1)

2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch (T2=) in response to TOF stimulation.

For reversal of rocuronium only:

16 mg/kg is recommended if there is a clinical need for reversal at 3 minutes following administration of doses of rocuronium up to 1.2 mg/kg.

Sugammadex was approved in the European Union (EU) in July 2008, and has been commercially available since September 2008.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for sugammadex (NDA 22225) relevant to this review:

- 10/31/2007: The Agency received a NDA 22225 submission for the routine reversal of shallow or profound neuromuscular blockage induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. The submission included a risk management plan consisting of routine labeling; the applicant did not submit a proposed REMS.
- 03/11/2008: Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) Meeting
 - The Committee unanimously recommended approval of sugammadex; however a detailed review of the drug hypersensitivity data was not available for discussion at the time of the meeting.
- 07/31/2008: The Agency issued a Not Approvable letter for the following deficiencies:

- The hypersensitivity reaction was not adequately studied in the drug development program
 - The effects of sugammadex on coagulation were not evaluated despite in vitro increases in coagulation markers
- 12/20/2012: The Applicant submitted a Complete Response to the Not Approvable letter (on 7/31/08). The submission included:
 - results of Study P06042 which was designed to evaluate the risk of hypersensitivity and anaphylaxis reactions, including repeat exposure anaphylaxis risk
 - results of Study P06315 which was designed to evaluate the risk of cardiac arrhythmias with sugammadex in combination with anesthesia
- 09/20/2013: The Agency issued a complete response letter due to the following findings by the Office of Scientific Investigations (OSI):
 - An audit conducted during the routine inspection by OSI indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data for Study P06042.
- 10/22/2014: The Applicant submitted a Complete Response to the CR Letter issued by the Agency (on 9/20/13)
 - Included were results of Study P101 which was designed to characterize the hypersensitivity and anaphylactic reaction, because the results from Study P06042 had been deemed unreliable
- 04/22/2015: The Agency issued a complete response letter due to the following findings by the OSI:
 - An audit conducted during the routine inspection by OSI indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P101
- 06/19/2015: The Applicant submitted a response to the Complete Response Letter issued by the Agency (on 10/22/14).
 - This submission is the subject of this review and contains no new Applicant initiated studies but does provide an updated safety database in a Periodic Safety Update Report
- 11/06/2015: Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to consider the following questions:
 - Whether the Applicant presented sufficient information to characterize the risk of hypersensitivity / anaphylaxis (13/14 voted yes)
 - Whether the Applicant presented sufficient information to characterize the risk of cardiac dysrhythmias (14/14 voted yes).

- Whether there are issues not addressed in the supportive data that warrant the need for additional studies and, if so, should these studies be conducted before or after approval.
- Whether the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of this application (14/14 voted yes).

3 Medical Condition(s) and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Residual neuromuscular blockade is defined as inadequate neuromuscular recovery as measured by objective neuromuscular monitoring. The train of four (TOF) method of peripheral nerve stimulation is a technique used during recovery from general anesthesia to objectively determine how well a patient's muscles are able to function. TOF is the application of electrical stimulation to nerves and recording of muscle response and is used when neuromuscular-blocking drugs have been part of the general anesthesia. The gold standard of acceptable neuromuscular recovery is a TOF ratio ≥ 0.9 ¹.

The residual effects of neuromuscular blocking agents (NMBA) may persist into the early postoperative recovery period and mild degrees of residual paresis (TOF ratios of 0.7-0.9) may be associated with significant impairment of respiratory and pharyngeal muscle function.² Complications associated with residual neuromuscular blockade include: an increased risk of aspiration, airway obstruction, hypoxia, and pharyngeal/esophageal complications, an increased risk of critical respiratory events and a significant prolongation of the length of stay in the post-anesthesia care unit (PACU).

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

NMBAs, given enough time after administration, will be metabolized and paralysis will cease. Currently, the recommendations for how to manage patients who will receive a NMBA during a procedure are that intermediate acting agents are used for neuromuscular blockade, that neuromuscular block is monitored and measured quantitatively throughout surgery, and that residual block is antagonized unless full recovery has been demonstrated using appropriate equipment.³ Time to full recovery will depend on the NMBA used during surgery.

Non-depolarizing NMBA induce paralysis by competing with acetylcholine at the post-junctional nicotinic receptors where they prevent changes in ion permeability of the skeletal muscle endplate and thereby prevent depolarization and subsequent contraction. The residual effect of NMBAs can be reversed by the administration of reversal agents. FDA approved reversal agents are anticholinesterases that increases the amount of acetylcholine at the junction, which can compete with the NMBA and

¹ Murphy GS, Brull SJ. *Anesth Analg*. 2010;111:120-8

² *Anesthesia & Analgesia* Volume 121(2), August 2015, p 366-372

³ Viby-Mogensen J. Postoperative residual curarisation and evidence-based anaesthesia. *Br J Anaesth* 2000;84:301-3.

ultimately restore impulse transmission and skeletal function. Since these agents have no effect on the NMBA concentration, this is an indirect mechanism for reversal and has a ceiling to its effectiveness.

Four products, pyridostigmine, edrophonium, edrophonium/atropine, and neostigmine are approved as reversal agents for the neuromuscular blocking effects of all available non-depolarizing NMBA. In the United States, neostigmine is the most commonly used reversal agent; it is preferred in clinical practice because of its more rapid onset of action compared to pyridostigmine and edrophonium. Neostigmine was approved by the FDA in January of 2015 for the reversal of the effects of nondepolarizing NMBAs after surgery.

The currently approved products have risk profiles that reflect the physiological effects of excess acetylcholine not only at the nicotinic but the muscarinic receptors as well. These reactions include severe bradycardia, copious secretions, increased gastrointestinal motility and bronchospasms. To mitigate these adverse events attributable to exaggerated pharmacological effects, an anticholinergic agent (e.g. atropine, glycopyrolate) should be administered prior to or concomitantly with the anticholinesterase reversal agents.

4 Benefit Assessment

The finding of efficacy for the reversal of neuromuscular blockade effects of sugammadex relied on four Phase 3 trials, two pivotal trials (301 and 302) and two primary trials (303 and 310) all submitted during the first cycle of review. The primary endpoint for studies 301, 302 and 310 was the elapsed time between the start of administration of the reversal agent and the recovery of the T4/T1 ratio to 0.9, as measured by acceleromyography. This endpoint is supported by a substantial body of evidence that T4/T1 ratio to 0.9 is clinically relevant and a safe range for extubation. The primary endpoint for study 303 was the elapsed time from the injection of the NMBA to recovery of T1 to 0.1 (“immediate reversal” endpoint). Secondary endpoints included clinical measures of recovery (i.e. 5-second head lift and general weakness) prior to PACU transfer after extubation and prior to PACU discharge. These clinical studies and their results are summarized below with tables adapted from Dr. Shibuya’s review⁴.

Table 1. Clinical trial synopsis	
Study	Study Design/Description
301	196 patients enrolled in a European study, November 2005 to March 2006, “shallow” neuromuscular block, defined as the return of T2 (the second twitch in a train-of-four stimulation) using 2mg/kg dose, primary endpoint was T4/T1 = 0.9 Treatment groups: A. Rocuronium/Sugammadex; B.

⁴ Shibuya, R. Clinical Review of EZVERA (NDA 22225), dated October 31, 2007.

	Rocuronium/Neostigmine; C. Vecuronium/Sugammadex; D. Vecuronium/Neostigmine
302	182 patients randomized in a US study November 2005 to November 2006, “profound” neuromuscular block, defined as 1-2 post tetanic counts using 4mg/kg dose, primary endpoint was T4/T1 = 0.9 Treatment groups: A. Rocuronium/Sugammadex; B. Rocuronium/Neostigmine; C. Vecuronium/Sugammadex; D. Vecuronium/Neostigmine
310	84 patients randomized in European Study November 2005 to Mary 2006, “shallow” neuromuscular block, defined as the return of T2 using 2mg/kg, primary endpoint was T4/T1 = 0.9 Treatment groups: A. Rocuronium/Sugammadex; B. Cisatracurium/Neostigmine
303	115 patients randomized to a US/Canadian study, February 2006 to August 2006, “Immediate” reversal (defined as 3 minutes following rocuronium administration) using 16mg/kg, primary endpoint was T1 = 0.1 Treatment groups: A. Rocuronium/Sugammadex; B. Succinylcholine/ No reversal

Table 2: Summary of pivotal efficacy data, primary efficacy endpoint, means (mm:ss)

Study #	Scenario	Org	Comparator	p-value
301	Routine	1:29 (R)	18:30	<0.0001
302	Routine	2:52 (R)	50:22	<0.0001
303	“Immediate”	4:22	7:04	<0.0001
310	Routine	2:02	8:46	<0.0001

To summarize, the efficacy studies conducted over the development program support the finding that sugammadex is effective for reversing rocuronium and vecuronium when administered as proposed. All efficacy studies showed statistically significant reductions in recovery times versus placebo and neostigmine. The studies also demonstrated less residual paralysis following sugammadex treatment

than neostigmine treatment; however, the residual paralysis was not associated with any differences in grip strengths, pulmonary function tests, or discharge from the PACU.

5 Risk Assessment

5.1 OVERALL SAFETY PROGRAM

The overall safety population consisted of pooled data from 58 trials with a total of 8900 subject exposures to IV study medications in 6121 unique subjects. Of these 5999 subject exposures were to IV sugammadex in 4453 unique subjects.

Consistent with Agency recommendations, two key pooled datasets were defined for analysis from the clinical program.

The first pooled dataset consists of data from all subjects who were administered anesthesia and/or an NMBA and who were exposed to sugammadex, active comparators or placebo (N=4145). This dataset is referred to as “Pooled Phase 1-3”.

The second pooled dataset consists of data from Phase 1 trials. Although most subjects were healthy, there were 21 unique subjects included in this group with renal impairment (study P105). All subjects included in this pooled group were exposed to sugammadex and/or placebo, but did not receive anesthesia or an NMBA. This dataset is referred to as “Pooled Phase 1”.

Pooled Phase 1-3 Trials

The incidence of serious adverse events (SAEs) in the sugammadex group was 5.3% (n=190/3601) and 7% (n=38/544) in the placebo group. Most SAEs were reported in the injury, poisoning and procedural complications in the System Organ Class (SOC) (61 [1.7%] subject exposures in the sugammadex group; 15 [2.8%] subject exposures in the placebo group.)

The injury, poisoning and procedural complications in the SOC include: post procedural hemorrhage, postoperative ileus, anastomotic leak, post procedural myocardial infarction, etc.

There were 13 subject exposures to sugammadex with resulting serious adverse events (SAEs) considered by investigators to be related to study drug. These SAEs include respiratory failure (1), atrial fibrillation (1), hypotension (1), ECG QT prolongation (3), abnormal QT interval (1), bronchospasm (2), hematoma (3), post-procedural hemorrhage (2), and psychotic behavior (1). In the placebo group the drug-related SAEs included ECG QT prolongation, hematoma, wound secretion, wound hemorrhage, and anemia.

Within this dataset, two subsets of pooled studies were defined to characterize the safety profile of sugammadex relative to placebo and neostigmine: “Pooled Placebo-controlled” and “Pooled Neostigmine-controlled”

Pooled Placebo-controlled

In the pooled placebo population similar incidence of SAEs associated with exposures across treatment groups with 6% (67/1078) and 7% (38/544) subject exposures in the sugammadex and placebo groups, respectively.

The highest incidence of exposures associated with SAEs were reported in the injury, poisoning and procedural complications SOC, with 17 (2%) subject exposures in the sugammadex group and 15 (3%) subject exposures in the placebo group. Drug-related SAEs were reported for 7 (1%) of subject exposures in the sugammadex group and 3 (1%) in the placebo group; of these, ECG QT prolongation was reported in 3 subject exposures to sugammadex and 1 for placebo.

Pooled Neostigmine-controlled

In the neostigmine controlled trials, SAEs were reported in 44 (5%) and 59 (7%) subject exposures in the sugammadex and neostigmine groups, respectively. The highest reported individual SAE occurred in 3 subject exposures in either treatment group: post procedural hemorrhage (3 subjects in the sugammadex group each exposed to 4 mg/kg sugammadex, and 0 in the neostigmine group), joint dislocation (no subjects in the sugammadex group and 3 in the neostigmine group), ileus and impaired healing (3 subjects in the sugammadex group and 3 in the neostigmine group), and supportive care (1 sugammadex, 3 neostigmine). Four subject exposures in the neostigmine group (procedural pain, acute myocardial infarction, pneumonia, delayed recovery) and 2 in the sugammadex group (post-procedural hemorrhage and hematoma) resulted in an SAE that was considered to be related to study drug by the investigator.

Pooled Phase 1

In the Pooled Phase 1 trials there were SAEs reported in 6 (0.3%) subjects in the sugammadex group versus 4 (0.3%) subjects in the placebo group. Three of the SAEs reported in the sugammadex group were considered by the investigators to be drug-related. Anaphylactic shock (urticaria, hypotension, tachycardia and flushing) and ECG QT prolongation accounted for two of the three SAEs and were both in the 16mg/kg group. The third SAE identified as drug-related was in trial P101 was a result of an accidental overdose of sugammadex, at 32mg/kg the subject experienced feeling hot, dysgeusia and headache.

From the clinical review⁵:

“In summary, the analysis of the severe adverse events occurring for the four treatment groups and various dose groups of sugammadex did not indicate that sugammadex was associated with greater risk for such events compared to placebo, neostigmine or succinylcholine or that the risk for such events was greater with increased doses of sugammadex.”

Deaths

⁵ Simone, Authur. Clinical Review NDA 22225, dated October 22, 2014.

In the overall sugammadex clinical development program, eight deaths have been reported. The Applicant notes that all of the deaths occurred after the trials were completed, and that none of them were considered drug-related according to the reporting investigators. Of the eight deaths, four followed sugammadex treatment.

From the clinical review⁵:

“In summary, the analysis of the deaths that occurred in the clinical development program does not indicate that sugammadex poses any greater risk than either placebo or neostigmine. There was a single death reported in the original NDA submission in which sugammadex may have played a role; however, with a near doubling of the safety database since that time, there is no additional evidence to suggest that sugammadex may increase patient mortality.”

The important safety concerns for sugammadex are: the potential for cardiac rhythm adverse events and anaphylaxis/hypersensitivity.

5.2 CARDIAC RHYTHM ADVERSE EVENTS

During the clinical studies, the occurrences of SAEs associated with QTc prolongation were more frequently seen in the sugammadex population than control population (placebo and neostigmine). In the original NDA submission, bradycardia, QTc interval prolongation, and tachycardia were reported more frequently than the other arrhythmias and these adverse events occurred more in sugammadex dose groups than did the others. Two dedicated QT/QTc studies were performed to measure potential effects of sugammadex alone (19.4.105) and sugammadex in combination with NMBA (rocuronium or vecuronium) (19.4.109). Both study results were submitted with the original NDA. A third study measured the potential effects of sugammadex in combination with anesthesia (sevoflurane or propofol) (P06315) and was included with the second NDA submission.

The Agency’s Interdisciplinary Review Team for QT Studies reviewed study 19.4.109 and concluded that although there was a concentration-dependent increase in the QT_c, the increase at the suprathreshold dose (32mg/kg) did not result in a clinically significant increase in the QTc interval. Overall, there was no evidence in these individual clinical trials that sugammadex alone (4 mg/kg or 32 mg/kg) or sugammadex (32 mg/kg) in combination with rocuronium or vecuronium caused an increase in QTc interval greater than 10 milliseconds, the level of regulatory concern according to the criteria of International Conference on Harmonization (ICH)-E14. Also, there was no evidence that sugammadex (4 mg/kg) caused an additional increase in QTc interval greater than 10 milliseconds when given in combination with either propofol or sevoflurane⁵. In addition there have been no reports of Torsade de pointes in either the clinical trials or the post-marketing setting.

During the clinical development program, for all doses of sugammadex, there was modestly greater proportion of patients who experienced a decrease in HR below 50 bpm and a dose trend for markedly decreased pulse rate/bradycardia. Bradyarrhythmias were the most commonly reported of the arrhythmias. A subset of these cases was identified as representing a distinct clinical pattern with onset of the events during the emergence phase of anesthesia shortly after administration of sugammadex. These cases generally responded to the standard administration of anticholinergic agents.

The medical reviewer concluded that “episodes of tachycardia and bradycardia that qualified as adverse events occurred following administration of sugammadex but not at frequencies that substantially differ from neostigmine or that exceeded that from placebo by a clinically relevant amount⁵.”

Bradycardia is addressed in the label in warnings and precautions with a recommendation to monitor for hemodynamic changes and to administer anticholinergic agents such as atropine if clinically significant bradycardia is observed.

The November 6, 2015 Advisory Committee unanimously agreed that the Applicant presented sufficient information to characterize the risk of cardiac dysrhythmias and that considerations have to be taken into context of the current practice and the role that sugammadex will play because current drugs for similar uses also have the potential to cause dysrhythmias.

5.3 ANAPHYLAXIS AND HYPERSENSITIVITY

In the original NDA submission, the clinical development program identified 7 subjects (of 1973 adults and 51 children) that experienced adverse events suggestive of anaphylaxis and drug hypersensitivity. Of those 7 cases, 3 met the diagnostic criteria for anaphylaxis; a frequency of 0.1%. The Applicant subsequently conducted a clinical study to evaluate skin prick testing (SPT) and intradermal skin testing (IDT) in 11 healthy volunteers with no prior sugammadex exposure and 12 patients with prior exposure. Of the 23 subjects tested, 2 had positive skin tests, and both were previously exposed to sugammadex. At this time there was no repeat-dose experience and concerns were raised that an increased risk of reaction upon re-exposure could not be ruled out. In order to better characterize the risk for hypersensitivity, two dedicated hypersensitivity trials were conducted (P101 and P06042). Findings from a 2013 audit of P06042 cited protocol deviations that could impact the validity, reliability and integrity of the data so the Applicant conducted a second trial (P101) with a similar design to that of P06042; this section will focus on study P101 and post-marketing reports.

Study P101 was a randomized, double-blind placebo-controlled parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration in healthy adult subjects. Overall, 7 subjects in the study discontinued treatment after experiencing hypersensitivity symptoms.

In the 16mg/kg sugammadex treatment group, 14 of 148 subjects experienced adjudicated hypersensitivity events (9.5%, 95% confidence interval: [5.3%, 15.4%]). In the 4mg/kg group, 10 of 151 subjects experienced adjudicated hypersensitivity events (6.6%, 95% confidence interval: [3.2%, 11.8%])

and only 1 of 76 subjects in the placebo treatment group experienced adjudicated hypersensitivity events (1.3%, 95% confidence interval: [0.0%, 7.1%]). The hypersensitivity AEs ranged from mild to moderate and 24 of the 25 subjects had symptoms that began within 1 hour and resolved within 24 hours after dose administration.

In a review⁶ from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), the reviewer identified 1 case of anaphylaxis in healthy subjects in study P101 which consisted of 299 unique subjects who received sugammadex.

From the review:

“As a result, we calculated a frequency of anaphylaxis of 0.33% (1/299) in a healthy volunteer population. It is of note that the case of anaphylaxis occurred on the first dose in the sugammadex 16mg/kg group.”

Sugammadex is administered by anesthesiology trained, skilled professionals in a controlled intraoperative setting capable of identifying and treating any hypersensitivity reaction. In addition, the hypersensitivity reactions were more frequently noted in the 16mg/kg dose group, with the first dose of sugammadex and occurred \leq 35 minutes after the dose was administered.

Given that anaphylaxis is the event of greatest clinical significance in the hypersensitivity spectrum, the Applicant included all post-marketing reports of anaphylaxis from countries that have approved sugammadex. The Applicant reports a total of 259 reports of anaphylaxis and 14 additional cases identified during hypersensitivity adjudication (total of 273 reports).

The most commonly described clinical feature in reports of anaphylaxis was dermatologic symptoms including urticaria, rash, erythema, flushing and skin eruption (183/273). The next most common feature was hypotension (181/273) and 157 patients were noted to require vasopressors for circulatory support. Sixty-six of the total 273 cases required further respiratory support, including re-intubation, prolonged intubation, manual or mechanical ventilation.

The AADPAC discussed the risks of anaphylaxis and 13/14 voted that the applicant presented sufficient information to characterize the risk of hypersensitivity/anaphylaxis and 14/14 voted that the efficacy, safety and overall risk-benefit profile of sugammadex supports approval.

Anaphylaxis will be included in the label in warnings and precautions with a recommendation to observe patients for an appropriate period of time after administration.

6 Expected Postmarket Use

Sugammadex is currently approved in 21 countries plus the EU (28 additional countries) and EEA (3 additional countries).

⁶ Torjusen, E. DPARP Memorandum for NDA 22225, dated March 20, 2015.

The post-marketing reports include data from market launch (July 25, 2008) to a cutoff date of April 22, 2015. The Applicant reports that over 12 million doses of sugammadex have been distributed in this time frame, with only (b) (4) returned to the suppliers.

Sugammadex will be given in an intraoperative setting by specialists (anesthesiology trained, skilled professionals) with all of the tools needed to manage adverse events. Given that roughly 90% of all surgeries utilize a NMBA, the potential patient population spreads across a wide variety of demographics.

Labeling

The most current version of the label highlights the following warnings and precautions: respiratory function monitoring, anaphylaxis, and marked bradycardia. Also mentioned are the waiting times for re-administration of NMBA and the recommendation to not use sugammadex in patients with severe renal impairment. The most common adverse reactions (reported in $\geq 2\%$ of patients and twice the placebo rate) highlighted in the label are cough, airway complication of anesthesia, anesthetic complication, procedural hypotension and procedural complication.

7 Discussion of Need for a REMS

Based on the currently available data, the benefit-risk profile for sugammadex is acceptable for the reversal of the effects of rocuronium bromide and vecuronium bromide (b) (4) surgery in adults. The safety concerns of interest are cardiac dysrhythmias, and anaphylaxis; these can be adequately managed through appropriate labeling. The prescribers/administrators of sugammadex will likely be specialists, specifically anesthesiologist or certified registered nurse anesthetists (CRNA), both of which are trained to monitor and treat intraoperative cardiac dysrhythmias and anaphylaxis. The safety concerns of interested are adequately addressed in labeling in warnings and precautions (anaphylaxis and bradycardia) in both the highlights section and the full prescribing information, therefore, a REMS is not needed to mitigate serious safety concerns of sugammadex.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sugammadex beyond routine measures.

A risk management plan was submitted with the first cycle, in which the Applicant concluded that “for all identified or potential risks, routine risk minimization activities are considered to be sufficient.”

9 Conclusion & Recommendations

In conclusion, risk mitigation measures beyond professional labeling are not warranted for sugammadex. Given that healthcare providers who are likely to use sugammadex are familiar with the risk of anaphylaxis and the importance of cardiac monitoring during the perioperative period, a REMS is not necessary to ensure the benefits of sugammadex outweigh its risk. Further assurance is provided given that sugammadex is administered in a controlled intraoperative setting equipped to treat medical emergencies. Should DAAAP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Deferral of Risk Evaluation and Mitigation Strategy (REMS) Review

Date: March 27, 2015

Reviewer(s) Leah Hart, Pharm.D., Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader Kim Lehrfeld, Pharm.D, DRISK

Deputy Division Director (Acting): Reema Mehta, Pharm.D, M.P.H., DRISK

Subject: Defer comment on DRISK evaluation of the need for a
REMS for sugammadex

Drug Name(s): Bridion (sugammadex)

Therapeutic class and Dosage Form Neuromuscular blockade reversal agent

Application Type/Number: NDA 22225

Applicant/sponsor: Organon USA Inc.

OSE RCM # 2015-706

*** This document contains proprietary and confidential information that should not be released to the public. ***

This memo is to defer Division of Risk Management (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Bridion (sugammadex), NDA 22225.

A 505(b)(1) application for Bridion was received by the Division of Anesthesia, Analgesia and Addictive Products (DAAAP) from Organon USA Inc. (Organon) on October 31, 2007. The application received a Complete Response (CR) on July 31, 2008, citing the following deficiencies:

1. The hypersensitivity reaction was not adequately characterized by the drug development program; and
2. The effects of sugammadex on coagulation were not evaluated despite in vitro increases in coagulation markers.

Organon responded to the CR (dated July 31, 2008) with a submission on December 20, 2012 that addressed the previous safety concerns with a new study. The application received another CR on September 20, 2013 due to findings during a routine inspection that could impact the validity, reliability and integrity of the data.

Organon responded to the CR (dated September 20, 2013) with a submission on October 22, 2014. The PDUFA date for the resubmission is April 22, 2015.

DAAAP has determined that the submission currently under review will likely receive a CR based on inspection findings; therefore, DRISK defers comment on the evaluation of the need for a REMS for Bridion (sugammadex) during this cycle. Evaluation of the need for a REMS for sugammadex will be undertaken by DRISK after the Applicant resubmits the NDA for review. Please send DRISK a new consult request at such time.

This memo serves to close the existing consult request to DRISK for Bridion (sugammadex) under NDA 22225.

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/s/

LEAH M HART-BANKS
03/27/2015

REEMA J MEHTA
03/27/2015
I concur.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 6, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Thru: Claudia Karwoski, Pharm.D., Acting Director
Office of Surveillance and Epidemiology (OSE)
Division of Risk Management (DRISK)

From: OSE Bridion RiskMAP Review Team
Scientific Lead: Jeanine Best, MSN, RN, PNP, Senior Drug Risk Management Analyst, OSE-DRISK
Mary Dempsey, Risk Management Coordinator, OSE-DRISK
Darrell Jenkins, Regulatory Project Manager, OSE-IO
Martin Pollock, PharmD, Safety Evaluator, OSE-DAEA

Subject: Review of Risk Management Plan

Drug Name(s): Bridion™ (sugammadex sodium injection)

Application Type/Number: NDA 22-225

Applicant/sponsor: Organon

OSE RCM #: 2007-2377

1 INTRODUCTION

This memorandum follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Bridion (sugammadex sodium) Injection Risk Management Plan (RMP) submitted to FDA by Organon on October 30, 2007, as part of the original New Drug Application (NDA) 22-225.

Sugammadex sodium, a modified cyclodextrin, belongs to a new class of selective relaxant binding agents (SRBAs), and was submitted for the indication: “for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium and for immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.”¹ Bridion Injection will be supplied as 2 and 5 mL vials containing 100 mg/mL of sugammadex for intravenous administration.

DAARP granted a Priority Review for this NDA because the mechanism of action of Bridion Injection may represent a significant advance over currently available reversal agents. Sugammadex sodium complexes with aminosteroidal neuromuscular blockers (specifically, rocuronium and vecuronium) and reduces the amount of the neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction, thus resulting in reversal of neuromuscular blockade.²

2 MATERIAL REVIEWED

- Risk Management Plan for ORG 25969 submitted with NDA 22-225, October 30, 2007

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Organon identified the following known risks with sugammadex sodium:

- Delayed onset time or insufficient neuromuscular blockade when a steroidal neuromuscular blocking agent is used too soon for re-treatment
- Prolongation of neuromuscular block occurring mainly from sub-optimal dosing and/or drug-drug interactions
- Re-occurrence of neuromuscular blockade occurring mainly from sub-optimal dosing and/or drug-drug interactions
- Use in patients with renal impairment because sugammadex sodium is cleared renally and exposure may be prolonged with decreased renal function

Organon identified the following potential risks with sugammadex sodium:

- Drug hypersensitivity (one clinical-trial subject developed symptoms consistent with a hypersensitivity reaction)
- Drug-drug interactions:
 - Hormonal contraceptives (capturing effect; sugammadex sodium may decrease progestin exposure similar to the progestin decrease seen when a daily dose of an oral contraceptive was missed).

¹ Cover Letter, NDA 22-225, Bridion™ (sugammadex sodium) injection, October 30, 2007

² Risk Management Plan for ORG 25969 submitted with NDA 22-225, October 30, 2007

- (b) (4) toremifene (displacement effect; potentially resulting in delayed reversal of neuromuscular blockade).

Organon identified the following important missing information with sugammadex sodium:

- Influence on laboratory parameters of blood coagulation time (prolonged) from in-vitro studies; clinical relevance unknown
- Pediatric exposure

3.2 POTENTIAL FOR MEDICATION ERRORS

- Wrong dose administered:
 - Low dose: potential for prolongation of neuromuscular blockade or re-occurrence of neuromuscular blockade
 - High dose: risks related to overdose are considered to be low given the wide therapeutic index of sugammadex sodium
- Wrong medication vial used: Organon plans to market Bridion Injection in vials that are distinct from rocuronium and vecuronium to prevent use of the wrong vial.

OSE/DMEDP (Division of Medication Errors and Prevention) will provide a separate review encompassing the tradename review and potential medication errors.

3.3 PROPOSED RISK MINIMIZATION ACTIVITIES

Organ proposes routine risk minimization activities including labeling (Package Insert, vial labeling), routine pharmacovigilance, and additional studies including a study in pediatric patients and further evaluation of hypersensitivity reactions. No additional risk minimization activities are planned at this time.

4 CONCLUSIONS

The Sponsor's submission does not constitute a formal Risk Minimization Action Plan (RiskMAP). We agree with the Sponsor that routine risk minimization activities for Bridion are adequate at this time based on the currently identified and potential risks of the product. No additional safety concerns have been identified at this time by either OSE or DAARP that warrant consideration of a formal RiskMAP or additional risk minimization activities.

If DAARP identifies additional safety concerns that warrant risk minimization activities above labeling and routine pharmacovigilance, or a formal RiskMAP, please re-consult OSE/Division of Risk Management.

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/s/

Mary Dempsey
3/6/2008 08:02:11 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/6/2008 12:11:49 PM
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