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Center for Drug Evaluation and Research
Food and Drug Administration
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Sent via Email: AADPAC@fda.hhs.gov

RE: FDA–2015–N–0001 Anesthetic and Analgesic Drug Products Advisory Committee; Notice of Meeting

To Whom It May Concern:

The American Association of Nurse Anesthetists (AANA) is the professional association representing more than 49,000 Certified Registered Nurse Anesthetists (CRNAs) and student registered nurse anesthetists nationwide. The AANA welcomes the opportunity to submit comments regarding new drug application (NDA) 022225, sugammadex sodium injection, submitted by Organon USA Inc., a subsidiary of Merck & Co., Inc., for the proposed indication of reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium.[1]

The AANA encourages the Anesthetic and Analgesic Drug Products Advisory Committee and the Food and Drug Administration (FDA) to approve sugammadex for clinical use in the United States. Sugammadex has been shown to be a safe and effective drug for the rapid reversal (3 minutes or less) of neuromuscular block induced by aminosteroidal neuromuscular blocking agents (NMBA) rocuronium and vecuronium.[2,3,4,5,6] Sugammadex has been used in clinical practice outside of the United States since 2008. The experiences of international clinical use offer anesthesia providers in the United States a better understanding of the applications and usefulness of sugammadex.

[1] Anesthetic and Analgesic Drug Products Advisory Committee; Notice of Meeting. Federal Register 80:177 (September 14, 2015) p. 55123.
[2] Yang LP, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. *Drugs*. 2009;69(7):919-942.
[3] Shields M, Giovannelli M, Mirakhur RK, Moppett I, Adams J, Hermens Y. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. *Br J Anaesth*. Jan 2006;96(1):36-43.
[4] de Kam PJ, van Kuijk J, Prohn M, Thomsen T, Peeters P. Effects of sugammadex doses up to 32 mg/kg alone or in combination with rocuronium or vecuronium on QTc prolongation: a thorough QTc study. *Clin Drug Investig*. 2010;30(9):599-611.
[5] Dahl V, Pendeville PE, Hollmann MW, Heier T, Abels EA, Blobner M. Safety and efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in cardiac patients undergoing noncardiac surgery. *Eur J Anaesthesiol*. Oct 2009;26(10):874-884.
[6] Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. *Core Evid*. 2013;8:57-67.

In a Cochrane systematic review of 18 randomized control trials (n=1,321 patients), Abrishami, et al. concluded that sugammadex was shown to be effective in reversing rocuronium-induced neuromuscular blockade when compared to placebo or neostigmine.[7] Serious complications occurred in less than 1% of the patients who received sugammadex.[7] Concerns have been expressed regarding the risk of drug-induced hypersensitivity reactions. A recent systematic review analyzed published and unpublished data identifying 15 cases, 10 of which were confirmed as developing sugammadex-induced hypersensitivity via skin prick testing.[8] These cases developed symptoms within 4 minutes of sugammadex and emphasize the importance of clinical vigilance especially during the initial administration of sugammadex.[9] Clinical studies have shown that other adverse effects are mild and short in duration, including spontaneous movement and taste alteration.[9] Considering the worldwide clinical use of sugammadex for over 6 years, the incidence of reported hypersensitivity is low.

The integration of sugammadex into clinical practice can have many advantages. Sugammadex has the ability to reverse neuromuscular block regardless of depth.[10,11] This can allow anesthesia providers to achieve deep (profound) neuromuscular block with a rapid and reliable reversal, even in cases with short duration. Sugammadex minimizes the risk of residual neuromuscular blockade that continues to be a clinical concern with the use of cholinesterase inhibitor reversal agents.[12,13,14] Improved and reliable restoration of motor function is particularly important for obese patients, who may be at increased risk of obstructive sleep apnea and airway obstruction, as well as elderly and acutely ill patients, who represent a large at-risk patient population. Post anesthesia issues such as hypoxia and inadequate ventilation are best addressed with assurance of full reversal and return of motor function after neuromuscular block.[15] The

[7] Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database Syst Rev*. 2009(4):CD007362.
[8] Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia*. Nov 2014;69(11):1251-1257.
[9] Welliver M, McDonough J, Kalynych N, Redfern R. Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. *Drug Des Devel Ther*. 2009;2:49-59.
[10] Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology*. Nov 2008;109(5):816-824.
[11] Sabo D, Jones RK, Berry J, et al. Residual neuromuscular blockade at extubation: A randomized comparison of sugammadex and neostigmine reversal of rocuronium-induced blockade in patients undergoing abdominal surgery. *Anesthe Clinic Res*. 2011;2(6).
[12] Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg*. Jul 2010;111(1):120-128.
[13] Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesth Analg*. Jul 2010;111(1):129-140.
[14] Murphy GS, Szokol JW, Avram MJ, et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. *Anesth Analg*. Jul 2013;117(1):133-141.
[15] Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg*. Jul 2008;107(1):130-137.

availability of sugammadex to immediately reverse rocuronium-induced neuromuscular block for intubation offers an alternative to succinylcholine used for difficult airway management or cases of short duration. Succinylcholine is a drug with significant side effects including myalgia, hyperkalemia, cardiac arrest, and malignant hyperthermia.[16,17] A more rapid and reliable reversal of neuromuscular block may support a decrease in recovery time and a more efficient utilization of perioperative resources.

AANA recommends that sugammadex be approved and available for clinical use as a reversal agent for rocuronium or vecuronium induced neuromuscular block. The unique drug action of sugammadex as a first in class selective relaxant binding agent enables improved options and opportunity to enhance anesthesia practice. Individual anesthesia providers are best suited to determine the choice of drug required for a particular case. Anesthesia providers, working with the patient team and facility, should balance patient-specific, safe and cost-effective care.

AANA recommends post-market surveillance of sugammadex use to continue monitoring safety and efficacy. AANA also recommends anesthesia provider education regarding the pharmacokinetics, contraindications, sensitivity or adverse reaction, and the importance of adverse drug event reporting for medication safety.

Sugammadex is a single drug reversal agent offering an improved safety profile without parasympathetic effects and an effective alternative to neostigmine and glycopyrrolate, given the recent concerns of price increases and shortages in the neuromuscular block reversal market.[18,19,20]

[16] Donati F, Bevan DR. Neuromuscular Blocking Agents. In: Barash PG, Cullen BF, Stoeling RK, Cahalan MK, Stock MC, eds. *Clinical Anesthesia*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:498-530.
[17] Hopkins PM. Malignant hyperthermia: pharmacology of triggering. *Br J Anaesth*. Jul 2011;107(1):48-56.
[18] American Society of Health-System Pharmacists. Neostigmine Methylsulfate Injection. http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?Id=1150. Accessed September 16, 2015.
[19] American Society of Health-System Pharmacists. Glycopyrrolate Injection. http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?id=385. Accessed September 16, 2015.
[20] Flamel Technologies. Flamel Technologies Announces Price Change for Bloxiverz. http://www.flamel.com/wp-content/uploads/2015/01/Flamel-Technologies-announces-price-change-for-Bloxiverz-20150115.pdf. Accessed September 16, 2015.

We thank you for the opportunity to comment on NDA 022225, sugammadex sodium injection. We look forward to continuing to serve as a resource to the FDA regarding any further anesthesia related issues. Please do not hesitate to contact Lynn Reede, CRNA, DNP, MBA, Senior Director, Professional Practice, at (847) 655-1136 or lreede@aana.com if you have any questions or comments.

Sincerely,

Juan Quintana, CRNA, DNP, MHS
AANA President

cc: Wanda O. Wilson, CRNA, PhD, AANA Executive Director/Chief Executive Officer
Lynn Reede, CRNA, DNP, MBA, AANA Senior Director, Professional Practice