American Society of Anesthesiologists®

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September 24, 2015

Randall P. Flick, MD, MPH
Chair
Anesthetic and Analgesic Drug Products Advisory Committee
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. FDA-2015-N-0001; New Drug Application (NDA) 022225, sugammadex sodium injection, before the Anesthetic and Analgesic Drug Products Advisory Committee

Dear Dr. Flick:

The American Society of Anesthesiologists (ASA), on behalf of 52,000 members, appreciates the opportunity to provide comments in response to the Food and Drug Administration's (FDA) September 14, 2015 Federal Register Notice regarding New Drug Application (NDA) 022225, sugammadex sodium injection, submitted by Organon USA Inc. (a division of Merck) for the proposed indication of reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium.

As an unbiased, scientific organization, ASA does not endorse pharmaceutical products. Moreover, Merck is an ASA corporate supporter and ASA's commercial support guidelines prevent ASA from making an actual or implied endorsement on behalf of any of its corporate supporters. Accordingly, this letter is intended to serve only as a resource for the FDA in determining the possible patient safety implications of a product with the clinically demonstrated properties of sugammadex.

Neuromuscular blocking agents, such as rocuronium or vecuronium, are administered to many patients receiving general anesthesia as a means to relax the muscles enough for the surgeons to work and to ensure that the patient does not move while anesthetized during delicate procedures. Before the patient can be awakened, however, an antidote to the NMB must be given so that the patient can move and breathe normally when the anesthetic is discontinued. For the past 50 years the only reversal agents available to physician anesthesiologists are from a class of drugs known as anticholinesterase inhibitors; these medications have limited efficacy. Therefore, there is a real clinical need for a class of medication that is biochemically designed to remove the most common NMBs (rocuronium or vecuronium) from the circulation in a highly predictable fashion. Such a drug may mitigate against the condition of inadequate reversal of NMBs which can lead to breathing complications in the recovery room. In addition, access to a faster acting reversal agent will enable the physician anesthesiologist to quickly reverse the NMB and restore spontaneous breathing in the rare situation where an adequate airway cannot be established in an anesthetized patient. As such, the availability of sugammadex, or a product with similar efficacy, may be life-saving for many patients each year.

With the increased application of novel surgical techniques, residual neuromuscular block induced by rocuronium or vecuronium continues to be a significant clinical and patient safety problem, and the incidence of undetected post-operative residual neuromuscular block (PORB) in the Post Anesthesia Unit (PACU) is much higher than most clinicians recognize.

Undetected PORB may be associated with adverse clinical consequences. In the great majority of healthy young patients, mild PORB (e.g., a TOF ratio of 0.70) generally can be tolerated without adverse consequences. Nevertheless, mild PORB has been associated with critical respiratory events upon arrival in the PACU,[1] an increased incidence of post-operative pulmonary complications,[2] delayed discharge times from the PACU,[3] and decreased pulmonary function (vital capacity and peak expiratory flow rate).[4] TOF ratios as high as 0.70-0.80 are associated with measurable dysfunction in the swallowing mechanism and the muscles of the upper airway. This places patients at increased risk of pulmonary aspiration. [5, 6]

Even minor degrees of PORB may not be tolerated by patients with decreased pre-existing pulmonary reserve, such as patients with emphysema, obstructive sleep apnea, myasthenia gravis, morbid obesity, advanced age, and painful upper abdominal or thoracic surgical incisions. A strong case can be made that in the above situations, a product with the clinically demonstrated properties of sugammadex would have the potential to improve patient safety.

Finally, world-wide experience over the last several years has shown that the side effects of sugammadex are very uncommon and usually of minimal clinical importance. While it is notable that there have been cases of anaphylaxis after administration of sugammadex,[7, 8, 9, 10] the exact incidence is unknown and such reactions are clearly rare since several million doses of the drug have already been administered. In fact, the incidence of rocuronium-induced hypersensitivity may exceed that of sugammadex.

ASA believes that there is a real need for a novel, unique drug to provide physician anesthesiologists with better capabilities to reverse NMB induced by rocuronium or vecuronium. It would significantly enhance the ability of physician anesthesiologists to more safely care for patients and reduce the incidence of critical respiratory adverse events in the PACU, especially for patients most at risk.

We look forward to continue working with the FDA on this important issue. Please feel free to contact Lisa Pearlstein, J.D. at l.pearlstein@asahq.org or 202-289-2222 if you have any questions or need any additional information regarding this issue.

Sincerely,

J.P. Abenstein, M.S.E.E., M.D.
President
American Society of Anesthesiologists

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[6] Eikermann M, Groeben H, Hüsing J, Peters J. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. Anesthesiology 2003; 98: 1333-7.

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