July 3, 2013

Anesthetic and Analgesic Drug Products Advisory Committee
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Docket No. FDA-2013-N-0001; New Drug Application (NDA) 022225, sugammadex sodium injection, before the Anesthetic and Analgesic Drug Products Advisory Committee

To Whom It May Concern:

The American Society of Anesthesiologists (ASA), on behalf of its over 50,000 members, appreciates the opportunity to provide comments in response to the Food and Drug Administration’s (FDA) May 10, 2013 Federal Register Notice regarding New Drug Application (NDA) 022225, sugammadex sodium injection, submitted by Organon USA Inc., for the proposed indications of routine reversal of moderate and deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at 3 minutes after administration of rocuronium. ASA strongly supports the approval of sugammadex for these indications because it will significantly enhance the ability of anesthesiologists to more safely care for patients due to its novel mechanism of action and its speed of reversal of non-depolarizing NMB.

There is a general consensus that satisfactory recovery from non-depolarizing NMB is defined by a train-of-four (TOF) ratio of 0.90 or higher measured at the adductor pollicis muscle of the hand by mechanomyography or electromyography.\(^1,2\) Residual neuromuscular block 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 Care Unit (PACU) is much higher than most clinicians recognize. Routine testing of neuromuscular function with a peripheral nerve stimulator is far from being practiced universally.\(^3,4\) Subjective (tactile, visual) detection of fade usually fails at TOF ratios >0.40,\(^5\) and only a small minority of clinicians in North America have monitors capable of quantifying the TOF ratio in real time. A review of numerous studies published in the last 10 years suggests that at least 10% of patients given an intermediate duration blocker will arrive in the PACU with TOF ratios ≤ 0.70 and over 25% of patients will arrive with TOF ratios < 0.90.
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, an increased incidence of post-operative pulmonary complications, delayed discharge times from the PACU, and decreased pulmonary function (vital capacity and peak expiratory flow rate). 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, placing patients at increased risk of pulmonary aspiration.

Neostigmine has limited efficacy for reversing deep NMB. Neostigmine works as a reversal agent by inactivation of acetylcholinesterase at the synaptic cleft, which increases the concentration of acetylcholine (ACh) available at the nicotinic receptor. This higher concentration of ACh relative to the blocking agent works toward restoring neuromuscular function. However, once the acetylcholinesterase is totally inhibited, there is a maximum amount of ACh that can be achieved at the synaptic cleft, and any remaining presence of blocking agent will continue to contribute to NMB. For that reason, neostigmine has limited efficacy in the presence of deep NMB.

In addition, even at modest neuromuscular block (a threshold TOF-count of 4), administration of neostigmine does not guarantee prompt and satisfactory return of neuromuscular function. To cite Kirkegaard, et. al., “It was not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration.”

In contrast, sugammadex is the only drug capable of antagonizing profound NMB (e.g. a post-tetanic count of 2) induced by vecuronium and rocuronium to full recovery in less than 3 minutes. This becomes particularly important as anesthetic and muscle relaxation requirements change with the application of novel surgical techniques (laparoscopic surgery, bariatric surgery, robotic surgery). These techniques place patients at increased risk of residual NMB because, in comparison to many other procedures, a deeper level of NMB is often required until the end of surgery. This need for profound relaxation significantly delays neostigmine-induced pharmacologic reversal, and markedly increases the incidence of PORB: neostigmine reversal from a TOF count of 1 may require as long as 76 minutes for recovery to a TOF > 0.90.

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. Because of sugammadex’s greater efficacy (compared to neostigmine), a strong case can be made that in the above situations, sugammadex has the potential to improve patient safety. Sugammadex is also potentially valuable in “can't intubate, can't ventilate” situations. This may occur in patients with unexpected difficult airways in whom rapid sequence induction with rocuronium was chosen.
Finally, based on the past 5 years world-wide experience, 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,\textsuperscript{15, 16, 17, 18} 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 sugammadex is a novel, unique drug that provides anesthesiologists better capabilities to reverse moderate and deep NMB. It is not just a “better” reversal agent, but one that provides a new paradigm for anesthesia care. Sugammadex will significantly enhance the ability of 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., Pain Medicine and Regulatory Lobbyist at l.pearlstein@asawash.org or 202-289-2222 if you have any questions or need additional information regarding this issue.

Sincerely,

\[Signature\]

John Zerwas, M.D.
President
American Society of Anesthesiologists


