Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Anesthetic and Life Support Drugs Advisory Committee

March 11, 2005

Hilton Washington DC/Silver Spring
Maryland Ballroom
8727 Colesville Road
Silver Spring, MD

I certify that I attended the March 11, 2008 meeting of the Anesthetic and Life Support Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Mimi T. Phan, PharmD, R.Ph	John T. Farrar, M.D.
Designated Federal Officer, ALSDAC	Acting Chair, ALSDAC

The Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 11, 2008 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background materials from the FDA and the Applicant. The meeting was called to order by John T. Farrar, M.D. (Acting Chair); the conflict of interest statement was read into the record by Mimi T. Phan, Pharm.D., R.Ph. (Designated Federal Official). There were approximately one hundred (100) persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: The committee discussed the new drug application (NDA) 22-225, sugammadex sodium injection, Organon USA Inc., for the proposed indication of routine reversal of shallow and profound neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at three minutes after administration of rocuronium.

Attendance:
ALSDAC Committee Members Present (Voting):
John T. Farrar, MD (Acting Chair); David G. Nichols, MD, MBA; Sulpicio de Guzman Soriano, III, MD

Special Government Employee Consultants (Voting):
Diane Aronson, BS (Acting Consumer Representative); Jayant K, Deshpande, MD, MPH; James C. Eisenach, MD; Nancy A. Nussmeier, MD; Julia E. Pollock, MD; Donald S. Prough, MD; Daniel Zelterman, PhD

Industry Representative (Non-Voting):
Charles McLeskey, MD (Acting Industry Representative)

FDA Participants (Non-Voting):
Mary Purucker, MD, PhD; Bob Rappaport, MD; Curtis Rosebraugh, MD; Robert Shibuya, MD; Arthur Simone, MD, PhD, Adam Wasserman, PhD

Designated Federal Official:
Mimi T. Phan, Pharm.D., R.Ph.

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**John T. Farrar, M.D.** Acting Chair, ALSDAC
Conflict of Interest Statement	**Mimi Phan, Pharm.D., R.Ph.** Designated Federal Officer, ALSDAC
Introduction to Meeting	**Bob Rappaport, M.D.** Director, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)/CDER/FDA

INDUSTRY PRESENTATIONS

Sugammadex: A Novel Reversal Agent for NMB

Introduction	**June Bray, M.B.A, R.Ph.** Vice President, Regulatory Affairs Organon, a part of Schering-Plough Corp.
Unmet Medical Need	**Ronald D. Miller, M.D.** Professor and Chairman, Department of Anesthesia and Perioperative Care School of Medicine University of California, San Francisco San Francisco, CA
Mechanism of Action, and Pharmacology and Pharmacokinetics	**Anton Bom, M.D., Ph.D.** Senior Research Fellow, Pharmacology, Organon, a part of Schering-Plough Corp.
Non-clinical Safety Overview	**Diels van Den Dobbelsteen, Ph.D.** Principal Toxicologist Organon, a part of Schering-Plough Corp.
Efficacy and Safety Clinical Overview	**Patrick Boen, M.D.** Senior Director Medical Services, Anesthesia Organon, a part of Schering-Plough Corp.

Summary	**Ronald D. Miller, M.D.**

Questions from the Committee

FDA PRESENTATIONS

Sugammadex: Efficacy and Outlier Analysis	**Robert B. Shibuya, M.D.** Medical Officer, DAARP/CDER/FDA
Sugammadex: Safety Considerations	**Arthur Simone, M.D., Ph.D.** Medical Officer, DAARP/CDER/FDA
Preclinical FDA Response	**Adam Wasserman, Ph.D.** Supervisory Pharmacologist DAARP/CDER/FDA

Questions from the Committee

Open Public Hearing (There were no requests to speak at the Open Public Hearing.)

FDA Summary of Issues	**Mary Purucker, M.D., Ph.D.** Medical Team Leader, DAARP/CDER/FDA

Questions to the Committee:

1. The Applicant has conducted a clinical trial to evaluate the efficacy of sugammadex to effect the "Immediate Reversal" of neuromuscular blockade (NMB). The primary efficacy endpoint was the time from start of administration of rocuronium bromide (RCB) or succinylcholine (Sux) to the recovery of T1 to 10% of its baseline value. Sugammadex was administered to patients 3 minutes following administration of RCB.

    a. Does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful?

The consensus of the committee was that the endpoint used, T1 = 0., was of minimal clinical use as it did not imply that a patient was ready to be extubated. By comparison, a T1 in the range of 0.7 to 0.9 was felt to be more clinically meaningful. The committee indicated that it would be more informative for clinicians to know the time when most (e.g., 95%) patients had fully responded. There was no consensus on this issue, but FDA was advised that obtaining this important information might be difficult. **(Please refer to the transcripts for details of the discussion.)**

    b. Based on the data submitted from this study, is there sufficient clinical information to assess whether sugammadex, when used with RCB, provides a clear advantage when confronted with a "cannot ventilate/cannot intubate" situation in the clinical setting? If not, what additional information would be required to assess a possible role for sugammadex in this scenario?

The committee agreed that sugammadex does offer some advantages in comparison to other neuromuscular blockade reversal agents, but other factors must be considered, including the induction agent and other concomitant medications used, and whether these were likely to interfere with spontaneous ventilation. The presence of co-morbidities such as upper airway anatomical abnormalities or pulmonary insufficiency would also be relevant. In addition, new technologies such as the LMA and combitube have been demonstrated to be useful in emergency settings such as the CICV scenario. It was noted that the sponsor did not address the obstetric patient population, where failed tracheal intubation is more likely, or those with renal insufficiency, where succinylcholine remains a necessary agent. The Committee recommended strongly that the sponsor fulfill a careful post-marketing surveillance and education plan regarding the obstetric and renal impairment subpopulations. **(Please refer to the transcripts for details of the discussion.)**

2. Based on the nonclinical data submitted by the applicant from the sugammadex distribution, juvenile animal, reproductive toxicology, and dedicated bone studies:

    a. Has the risk for adult patients, including patients with fractures or surgical injury to bone, been adequately characterized?

The consensus from the committee was that there is no evidence suggesting a problem for adult patients, but given that bone changes occurred in adult and young animals, there may be potential for risk in adults with bone fractures. A post-marketing surveillance plan should be implemented if sugammadex is approved. **(Please refer to the transcripts for details of the discussion.)**

    b. Has the risk for pediatric patients been adequately characterized?

The committee felt that the risk in the pediatric patient population has not been adequately characterized. They suggested that the sponsor first complete a long-term repeated-dose exposure study in young animals to understand the wash-out period better, and for a longer wash-out than 172 days, and to understand the effects of receiving the agent with some regularity over a longer time period to determine if repeated exposure over time would lead to significant risk. The committee also felt that additional studies of sugammadex's effects on bone fractures in juvenile animals would be useful, including data on the uptake of the drug, as well as the healing process, at the fracture site. Additionally, evaluation of the bone strength of mature animals after repeated juvenile exposure would be necessary to characterize and define the risk to pediatric patients.

In addition, because the immature renal function in the neonatal or infant pediatric population is different from the renal function of the young rats and rabbits studied, the Committee recommended that the sponsor investigate further the effect of sugammadex on pediatric renal function and that nonclinical studies in an immature renal function model may be appropriate. **(Please refer to the transcripts for details of the discussion.)**

    c. Does the nonclinical data support the safety of sugammadex for clinical trials in a pediatric population?

The committee felt that there are enough data on single-dose exposures to suggest that single-dose clinical trials would be reasonably safe, but clearly there are concerns about repeated exposures. Multi-dosing studies in pediatric patients should not occur until all the reproductive toxicity and juvenile studies have been thoroughly analyzed. Additional data, including a juvenile rat study with bone strength (i.e., load-bearing) assessment, would be important to support multiple-dose clinical trials. **(Please refer to the transcripts for detail discussions)**

d. If the answers to any of the above questions is "no," what additional information is required to support the use of sugammadex in these populations?

This question was not directly addressed, but the discussion was covered in the answers to 2b and 2c.

3. Has the applicant adequately demonstrated that sugammadex:
   a. Reverses neuromuscular blockade from rocuronium and vecuronium;

   Yes: 10 ***No: 0*** ***Abstain: 0***

   b. Immediately reverses neuromuscular blockade from rocuronium?

The Agency withdrew this question for voting, but received comments from the committee. The committee agreed that studies with sugammadex do support its proposed indication of reversal from rocuronium, but the majority of the panel agreed that the word "immediately" should be replaced by a description of the clinical trials and their findings. This would be more informative to the practitioner, who may then determine whether sugammadex is appropriate for use in an urgent circumstance. **(Please refer to the transcripts for details of the discussion.)**

   c. Can be used safely in the targeted population? Please discuss potential hypersensitivities in this population, if patients at risk cannot be identified.

The Agency clarified "targeted population" as adult patients receiving rocuronium or vecuronium, excluding patients with renal impairment. The Committee suggested also excluding obstetric and pediatric patient populations, until additional studies are available for these two populations. The Committee discussed the issue of the potential for hypersensitivity to the agent. The Committee agreed that the rates of potential hypersensitivity symptoms appeared to be similar between the drug and the placebo group, but because there were few patients on placebo, small differences would not be detected. It was also agreed that none of the cases identified with potential hypersensitivity required additional therapy. However, it was also agreed that the available data did not preclude the possibility of some level of hypersensitivity reaction, and that this should be carefully followed with post-marketing surveillance, if sugammadex is approved. **(Please refer to the transcripts for details of the discussion.)**

Yes: 10 ***No: 0*** ***Abstain: 0***

The meeting adjourned for the day at approximately at 4 p.m.