

Sugammadex (BRIDION) National Drug Monograph August 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/Mechanism of Action

Sugammadex is a gamma cyclodextrin agent that has been modified. It acts by limiting the amount of neuromuscular blocking drug that is available to bind nicotinic cholinergic receptors by forming a complex with rocuronium or vecuronium. This action results in reversal of the neuromuscular blockade (NMB) caused by rocuronium and vecuronium.

Indication(s) Under Review in this document (may include off label)

Sugammadex is indicated for the reversal of neuromuscular blockade (NMB) induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.

Dosage Form(s) Under Review

Single dose vial for injection:
200 mg/2 mL (100 mg/dL) or
500 mg/5 mL (100 mg/mL)

REMS

REMS No REMS Post-marketing Requirements

Pregnancy Rating

No evidence in humans and no specific recommendations provided. Therefore, the risks of sugammadex to the fetus must be weighed against the benefits to the mother.

Executive Summary

Efficacy

- There are ten trials comparing the time to achieve pharyngeal and respiratory muscle recovery from neuromuscular blockade (NMB) as assessed by quantitative monitoring of the adductor pollicis (thumb) muscle and reaching a train of four (TOF) ≥ 0.9 ; which is considered to be near full neuromuscular recovery between sugammadex and neostigmine or edrophonium.
- In the trials, patients were generally younger and relatively healthy with a mean age of 50 years or less and American Society of Anesthesiologists (ASA) health status of I-II (healthy to mild systemic disease) in most trials.
- Time to achieve near full recovery to the point where reoccurrence of NMB or residual NMB is unlikely (TOF ≥ 0.9) was less than 3 to 5 minutes for sugammadex in most patients and ranged from less than 10 min up to 50 minutes for neostigmine.
- Although the trials were not designed to identify differences in clinical outcomes, outcomes in the post-anesthesia care unit (PACU) and beyond were recorded. There were no clear consistent differences between sugammadex and neostigmine in terms of being awake, alert and oriented, ability to perform muscle related tasks such as 5 second head lift, or consequences of residual NMB after reversal.
 - In the study by Carron, et al. in 40 morbidly obese patients, mean time

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	<p>to tracheal extubation did not differ (Suga 8.6 vs. Neo 9.85 min, p=0.08) but ability to swallow after extubation occurred more quickly with sugammadex vs. neostigmine (7.1 vs. 12.2 min, respectively, p=0.003), ability to get into bed independently was faster with sugammadex vs. neostigmine (24 vs. 33 min, respectively, p=0.02), and time in PACU was less with sugammadex vs. neostigmine (37 vs. 48 min, respectively, p=0.01).¹⁹</p> <ul style="list-style-type: none"> ○ In a study by Geldner, et al. in 140 patients with various levels of NMB undergoing laparoscopic surgery, time from admission to the operating room (OR) to discharge ready did not differ between sugammadex and neostigmine nor did the time from admission to the PACU to being considered ready for discharge from the PACU. However, time from drug administration to tracheal extubation and time from drug administration to being ready to discharge from the OR was shorter in the sugammadex vs. neostigmine groups (mean treatment difference between groups was approximately 6 and 6.5 minutes).²¹ In this study, the authors concluded that they were not able to show a difference in overall duration of time spent in the OR or the PACU. And, earlier tracheal extubation did not translate into more rapid discharge, but there may have been other factors preventing a difference in this outcome. ● It is unclear whether routine use of sugammadex vs. neostigmine will result in improved outcomes since evidence is lacking. Additionally, it is unclear if quantitative monitoring is consistently used to monitor neuromuscular recovery to TOF=\geq0.9 after reversal with neostigmine will result in different outcomes when compared to reversal with sugammadex with or without quantitative monitoring. As a result, until more clinical data is available, it would be prudent to reserve this agent for patients in whom a higher risk for residual NMB and its complications are expected, or for patients where succinylcholine should be avoided (described in detail under “Projected Place in Therapy”).
Safety	<p><u>Hypersensitivity/Anaphylaxis</u>: The severity of these reactions can vary from isolated skin reactions to serious systemic reactions (anaphylaxis and anaphylactic shock).</p> <ul style="list-style-type: none"> ○ Anaphylaxis has been reported in 0.3% of healthy volunteers. Patients should be monitored for an appropriate duration after administration of sugammadex. ○ Providers should be aware that in trials where anaphylaxis occurred, it was frequently associated with life-threatening cardiovascular events requiring immediate and aggressive management. ○ Severe hypersensitivity reactions have occurred in patients with no prior exposure to sugammadex. ● Significant <u>bradycardia</u> has been reported within minutes of administration of sugammadex; some cases of which have resulted in cardiac arrest. ● Patients must be provided with ventilatory support until adequate spontaneous respiration has been restored and a patent airway is ensured. In the event that neuromuscular blockade persists or recurs following removal of ventilatory support, steps must be taken to provide sufficient ventilation. ● Recurrence of neuromuscular blockade was observed in <1% of patients following an appropriate dose of sugammadex for reversal of rocuronium or vecuronium. <p>Sugammadex was submitted for approval in 2008 but was not approved for use in the United States since there were safety concerns associated with hypersensitivity reactions and anaphylaxis upon repeat exposure and a lack of information on the effect of sugammadex on clotting and perioperative bleeding.</p> <ul style="list-style-type: none"> ○ The Division of Pulmonary, Allergy, and Rheumatology Products

	<p>(DPARP) concluded that sugammadex can cause hypersensitivity reactions and anaphylaxis and the risk seems to increase with the use of higher doses. Repeated doses of sugammadex did not appear to increase the risk for or the severity of these reactions. The rate of hypersensitivity reactions with sugammadex compared to other drugs used in the operative setting is unclear. Therefore, a benefit-risk assessment must be made when determining use of sugammadex.</p> <ul style="list-style-type: none"> ○ The Division of Hematology Products (DHP) concurred that in a study of patients undergoing orthopedic surgery of the lower limb and receiving heparin thromboprophylaxis, there was no evidence that sugammadex versus usual care (neostigmine) increased the frequency of hemorrhage despite some prolongation of aPTT and PT (lasting for under sixty minutes) after sugammadex administration. From the evidence reviewed, DHP concluded that the risk for postoperative bleeding after administration of sugammadex is not higher than that following neostigmine or spontaneous recovery from rocuronium or vecuronium. ● Adverse reactions reported by $\geq 10\%$ of patients and at a greater rate than placebo include vomiting, nausea, hypotension and headache. Adverse events do not appear to be dose-dependent with the exception of potentially anaphylaxis, hypersensitivity reactions and dysgeusia, which occurred at a higher frequency with the 16 mg/kg dose vs. the 2 or 4 mg/kg doses.
Other Considerations	<p>Post-marketing surveillance identified the following adverse events:</p> <ul style="list-style-type: none"> ● Cardiac disorders including marked bradycardia and cardiac arrest associated with bradycardia occurred within minutes of sugammadex administration. Others reports of cardiac events include atrial fibrillation, atrioventricular (AV) block, cardiac/cardiorespiratory arrest, ST segment changes, supraventricular tachycardia/extrasystoles, tachycardia, ventricular fibrillation and ventricular tachycardia. ● Circumstances where sugammadex did not have the intended reversal effect. ● Reports of severe hypersensitivity including anaphylactic shock, anaphylactic and anaphylactoid reactions. ● Reported cases of laryngospasm, dyspnea, wheezing, pulmonary edema and respiratory arrest have occurred in association with sugammadex. ● Because these reports are voluntary, a causal relationship or frequency of occurrence is unknown. <p>There have been several retrospective, cost-effectiveness studies examining use of sugammadex. Two reports found that sugammadex may be cost-effective if time saved is limited to the operating room. However, if time is saved in the recovery room, it was not considered to be cost-effective. In one study, use of sugammadex in higher risk patients (e.g., elderly, morbidly obese, neurologic, neuromuscular, respiratory, cardiac, kidney or liver impairment) was felt to be cost-effective.</p> <p>Sugammadex can be used to reverse various levels of neuromuscular blockade induced by rocuronium or vecuronium. The dose of sugammadex does not depend upon anesthetic regimen. *Note: sugammadex should not be administered to reverse NMB caused by benzylisoquinolinium agents (e.g., atracurium and cisatracurium) since it is not effective for reversing these agents. Additionally, under dosing should be avoided since it can lead to suboptimal reversal of NMB or reoccurrence of NMB.</p>
Projected Place in Therapy	<ul style="list-style-type: none"> ● Residual NMB can lead to the need for re-intubation, impaired oxygenation and pulmonary function, increased risk for aspiration and pneumonia, pharyngeal impairment, unpleasant muscle weakness and a delay in being discharged from the PACU. The risk for complications from residual NMB increase with age, morbid obesity, obstructive sleep apnea, and respiratory impairment and in those

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	<p>patients with poorer health status. Although evidence is lacking to support improved outcomes with sugammadex vs. neostigmine, there is low quality evidence to suggest that sugammadex may result in improved outcomes in higher risk groups such as those patients with reduced pulmonary reserve, morbid obesity, obstructive sleep apnea, advanced age and ASA physical status of 3 or 4. However in one study by Todd, et al., after implementing an extensive educational program and use of quantitative monitoring after reversing NMB with neostigmine, the number of re-intubations with appropriate monitoring over a period of more than 2 years went from 2-4 per year without monitoring to none with appropriate quantitative monitoring.</p> <ul style="list-style-type: none"> • Sugammadex reduces NMB more quickly than neostigmine but prospective evidence is lacking to support an improvement in respiratory or other outcomes when used routinely over neostigmine. However, the risk for residual or reoccurrence of NMB may be increased in certain higher risk patients (advanced age, ASA status 3 or 4, morbid obesity, obstructive sleep apnea, reduced pulmonary reserve and overall poorer health), especially when quantitative monitoring is not utilized routinely, and therefore the use of sugammadex may be appropriate in selected high-risk individuals. Additionally, the use of sugammadex may be appropriate when surgical cases necessitate deep NMB throughout the duration of the procedure and rapid reversal is needed or when use of succinylcholine should be avoided (e.g., Trauma, prolonged immobilization (up-regulation of nicotinic receptors), muscular dystrophies, severe burns (>48 hours after burn), crush injury, renal failure, polyneuropathies, etc. (Settings in which admin. can lead to hyperkalemia). • As a result, until more clinical data are available, it would be prudent to reserve this agent for patients in whom a higher risk for residual NMB and its complications are expected, or for patients where succinylcholine should be avoided, as follows: <ul style="list-style-type: none"> ○ Conditions in which patients may be at higher risk for residual NMB and its complications where sugammadex may be preferred over neostigmine: Morbid obesity, obstructive sleep apnea, advanced age, poorer health status (ASA physical status of 3 or 4), impaired pulmonary function, need for deep neuromuscular block throughout operative procedure, surgeries ending abruptly or sooner than expected, cannot-intubate, cannot-ventilate settings, etc. ○ Conditions in which patients may be at higher risk for severe hyperkalemia or malignant hyperthermia where succinylcholine should be avoided for RSI: Trauma, prolonged immobilization, neuromuscular disorders, >48 hours after severe burns, crush injuries, renal failure, etc.
Potential Impact	<ul style="list-style-type: none"> • There is a significant increase in drug cost with sugammadex vs. neostigmine plus glycopyrrolate or atropine for reversing NMB. • It is unclear if selected use of sugammadex in high-risk patients for residual NMB will result in improved outcomes. • It is possible that availability of sugammadex for use in selected high-risk patients will result in greater use of rocuronium or vecuronium in place of cis-atracurium in these patients.

Background

Purpose for review

Sugammadex was approved in December 2015 for the reversal of blockade induced by rocuronium bromide or vecuronium bromide in adults undergoing surgery. Sugammadex was approved for use in 48 countries as of April 2014. It is now approved for use in 58 countries worldwide.

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Issues to be determined:

- ✓ Evidence of need
- ✓ Does sugammadex offer advantages to currently available alternatives?
- ✓ Does sugammadex offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does sugammadex have specific characteristics best managed by the non-formulary process, prior authorization or criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance (Comments)
Neostigmine Methylsulfate	Most commonly used nondepolarizing neuromuscular blocking reversal agent	--
Pyridostigmine Bromide	Nondepolarizing neuromuscular blockade reversal agent	Not generally used for reversing NMB due to slow onset of effect (>16 min)
Edrophonium Chloride	Nondepolarizing neuromuscular blockade reversal agent	--
Succinylcholine	Depolarizing neuromuscular blocking agent with short duration of effect and no reversal agent	--
Atropine	Anticholinergic	Used to reduce the muscarinic effects of anticholinesterase reversing agents
Glycopyrrolate	Anticholinergic	Used to reduce the muscarinic effects of anticholinesterase reversing agents
Non-formulary Alternative (If applicable)	Other Considerations	

Efficacy (FDA Approved Indications)**Literature Search Summary**

A literature search was performed on PubMed/Medline (1966 to March 2016) using the search terms sugammadex, neuromuscular blockade reversal and Bridion. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials and medical reviews and transcripts of FDA advisory committees available on the FDA website were also reviewed. The AMCP dossier was reviewed for relevant information and the clinicaltrials.gov site was searched for planned, ongoing and completed trials pertaining to sugammadex. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

The FDA approval of sugammadex (BRIDION®) was based upon review of four pivotal trials conducted in the United States, Europe and Canada.^{14-16,23} These trials were conducted in patients undergoing surgical procedures requiring varying levels of neuromuscular blockade (NMB) and compared the time to reversal of NMB with neostigmine or sugammadex or time to reversal with sugammadex versus spontaneous recovery after succinylcholine.² In each of the studies, the acetylcholinesterase inhibitors (neostigmine and edrophonium) were administered with an anticholinergic agent (atropine or glycopyrrolate) to minimize the muscarinic or cholinergic side effects. In most trials, patients were younger and relatively healthy with a mean age of 50 years or less and an American Society of Anesthesiologists (ASA) health status of I-II (healthy to mild systemic disease). In general,

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patients with anticipated difficult intubation; those with known or possible neuromuscular disorders; known allergy or sensitivity to study drugs or receiving potentially interacting drugs were excluded from studies. In a number of studies, at least a few patients receiving neostigmine did not reach TOF=0.9 during the observational period (e.g., 30-60 min, until the patient was awake, etc.). Finally in several of the trials, achievement of a TOF=0.9 after administration of sugammadex was delayed significantly in some patients (up to 22 minutes vs. the typical <5 min NMB reversal).³

There are certain surgical settings in which achieving deep NMB is necessary to adequately perform the surgical procedure, including ear nose and throat, thoracic, neurosurgical and laparoscopic surgery. Sugammadex was compared to neostigmine for reversal of profound or deep NMB in several studies.^{16-17, 19, 21} Acetylcholinesterase inhibitors, including neostigmine are not sufficiently effective for reducing deep NMB since the concentration of acetylcholine at the receptor is inadequate to displace the NMB drug from its binding sites. Therefore, there is a waiting period for reappearance of the second twitch in the train of four monitoring before neostigmine can be given to effectively reverse NMB. Alternatively sugammadex sequesters the aminosteroid NMB drug, forms an inactive complex that is removed from the body and quickly reverses deep NMB.

No trials were identified for reversing NMB in the intensive care setting.

(For trial details, refer to Table 1 and Table 2)

Efficacy Measures:

The use of more objective, quantitative measures for monitoring resolution of NMB is increasingly recognized as being important because of the relatively high numbers of patients with residual NMB arriving in the post anesthesia care unit (PACU) when more subjective measures of recovery are used (e.g., 5 section head lift, eye opening, protrusion of the tongue, grip strength, nerve stimulator without objective quantitative monitoring, etc.).⁴⁻⁹ Residual NMB can lead to the need for re-intubation, impaired oxygenation and pulmonary function, increased risk for aspiration and pneumonia, pharyngeal impairment, unpleasant muscle weakness and a delay in being discharged from the PACU.⁶⁻⁹ The risk for complications from residual NMB increases with age, morbid obesity, obstructive sleep apnea, respiratory impairment and in those patients with poorer health status.⁹⁻¹⁰ The risk for residual NMB has been shown to be higher in cases where the eye muscle was monitored for recovery versus monitoring of the adductor pollicis muscle (52% vs. 22%, respectively. Adjusted odds ratio 5.5, 95% CI 2.1-14.5).¹¹⁻¹² The risk for residual NMB has also been shown to be higher when qualitative monitoring was compared quantitative monitoring using acceleromyography (50% vs. 14.5%, respectively $p < 0.0001$) for recovery but clinical signs of muscle weakness were small and did not differ between groups.⁷ There are several trials that have shown a reduction in residual NMB when quantitative vs. qualitative monitoring of recovery was used and when reversal agents were used compared to when they were not used.²⁵⁻²⁷ In the study by Todd, et al., 2-4 re-intubations per year in the post anesthesia care unit (PACU) were probably or possibly related to incomplete NMB reversal.²⁶ After an extensive educational program and implementation of quantitative monitoring, use of the monitoring device increased significantly and there were no cases of re-intubation in the PACU in the two years after implementation. Todd, et al., reported in a follow-up letter to the editor which described two cases of residual or recurrence of NMB reversal since implementation of quantitative monitoring. A review of those two cases revealed that neither case was properly monitoring for NMB reversal.²⁸

- Train-of-Four (TOF) quantitative monitoring of recovery from NMB: Measures the force of contraction of the adductor pollicis muscle (thumb) in response to electrical stimulation of the ulnar nerve. Four stimuli are administered and separated by 0.5 seconds. When non-depolarizing muscle blockers are used, there is a “fade” phenomenon between the first stimuli and the fourth. The degree or stage of recovery is determined based upon the ratio of the fourth twitch to the first twitch (T4/T1). TOF=1 is completely normal, TOF ≥ 0.9 correlates with recovery of the upper airway muscles indicating recovery from NMB adequate for respiratory function. Therefore, the time to reach a TOF ≥ 0.9 was the primary outcome measure in most of the studies and serves as a key criterion for determining adequate recovery from NMB and the decision to extubate.

Table 1. Clinical Trials of Sugammadex for Reversing Neuromuscular Blockade after Surgery

Clinical Trial	Population/ Intervention	Primary Endpoint/ Monitoring	Results	Adverse Events/ Comments
Sacan, et al. ¹³ OL, R N=60 (20 in each group)	ASA status I-III Suga 4 mg/kg, Neo 70 mcg/kg+glyco 14 mcg/kg OR Edro 1 mg/kg+A 10 mcg/kg Each admin 15 min after last dose of rocur	Time to achieve TOF=0.9 <u>Monitoring:</u> acceleromyograph: AP muscle	<u>Mean Time to reach TOF=9:</u> Suga: 1.78 min Neo: 17.4 min Edro: 5.52 min (p<0.05 for both vs. Suga) <u>Pts reaching TOF=0.9 in 30 min observation:</u> Suga: n=20/20 Neo: n=5/20 Edro: n=2/20	Pt preferring not to receive investigational agent were R to Neo or Edro. Unclear if admin of Neo or Edro occurred after at least 1-2 twitches were present. 1 pt in Suga vs. 4 Neo and 2 Edro reported general muscle weakness. No diff, in ability to perform 5 sec head lift. No differences in safety
Blobner, et al. ¹⁴ R, safety observer blinded N=98 (49 in each group)	ASA status I-III (96% of pts ASA I-II) Suga 2mg/kg or Neo 50 mcg/kg+glyco 10mcg/kg were given at reappearance of T ₂ after stopping rocur	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle	<u>Median Time to reach TOF=0.9:</u> Suga: 1.4 min Neo: 18.5 min, p<0.0001 98% of pts achieved TOF=0.9 reached in 5 min Suga vs. 11% with Neo. Took 101 min for 98% of Neo pts to achieve TOF=9 <u>Median rocur dose admin:</u> Suga: 46 (29-94) mg Neo: 50 (31.8-178) mg	98% of Suga and 94% of Neo included in primary endpoint. Clinical signs of neuromuscular function did not differ (awake and oriented, cooperative, etc.). No evidence of residual block or reoccurrence in either group. No differences in safety
Khuenl-Brady, et al. ¹⁵ R, safety observer blinded N=100 (51 Suga vs. 49 Neo)	ASA status I-III (93-94% of pts ASA I-II) Suga 2mg/kg or Neo 50 mcg/kg+glyco 10mcg/kg were given at reappearance of T ₂ after stopping vecur	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle	<u>Mean Time to reach TOF=0.9:</u> Suga: 2.7 min Neo: 17.9 min, p<0.0001 <u>95th percentile TOF=0.9:</u> Suga: 6.96 min Neo: 76.15 <u>Awake and oriented prior to transfer to recovery.</u> Suga: 60.4% Neo 57.8%	No serious ADEs were reported. No reoccurrence or NMB or residual NMB was reported. Upon discharge from recovery, all but one in Neo group were awake, oriented, cooperative and able to perform 5 sec head lift.
Jones, et al. ¹⁶ R, safety observer blinded N=74 (37 in each group)	ASA status 1-IV (76-87% of pts ASA I-II) Suga 4 mg/kg or Neo 70 mcg/kg+glyco 14 mcg/kg were given at 1- 2 post-tetanic counts after stopping rocur (<i>Profound NMB</i>)	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle	<u>Median Time to reach TOF=0.9:</u> Suga: 2.7 min Neo: 49 min, p<0.0001 70% of Suga met TOF= \geq 0.9 in 3 min or less. In Neo, 73% recovered within 30-60 min and 23% taking >60 min to achieve TOF= \geq 0.9	No serious ADE reported. Data were missing from 1 Suga and 15 Neo pts because TOF= \neq 0.9 was not reached during observation period. Upon discharge from recovery, all but one in Neo group were awake, oriented, cooperative and able to perform 5

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			<u>Awake and oriented prior to transfer to recovery.</u> Suga: 70% Neo: 59%	sec head lift.
Lemmons, et al. ¹⁷ R, safety observer blinded N=94 (52 Suga vs. 42 Neo)	ASA status 1-IV (64-87% of pts ASA I-II; 36% ASA III in Neo vs. 13% in Suga) Suga 4 mg/kg or Neo 70 mcg/kg+glyco 14 mcg/kg were given at 1- 2 post-tetanic counts after stopping vecur (<i>Profound NMB</i>)	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle	11 pts discontinued study before study drug given (5 Suga, 6 Neo) <u>Median Time to reach TOF=0.9:</u> Suga: 3.3 min Neo: 49.9 min, p<0.0001 All but 9 Suga and 10 Neo pts were cooperative and performed the 5 sec head lift and tests to determine muscle weakness before transfer to recovery.	1 pt in Neo reported anxiety, depression and anger that the investigator thought may be related. No difference in clinical signs of recovery between groups. No other serious ADEs
Illman, et al. ¹⁸ R, DB N=50	ASA status I-IV Suga 2mg/kg or Neo 50 mcg/kg+glyco 10mcg/kg were given at reappearance of T ₂ after stopping rocur	Time gap from loss of visual fade to return of TOF=0.9 (Unsafe period) Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle. And, visual monitoring of the twitch response.	<u>Time gap from loss of visual fade to return of TOF=0.9 (Unsafe period)</u> Suga: 0.3 min Neo: 10.3 min, p<0.001 <u>Time to reach TOF=0.9</u> Suga: 1.7 min Neo: 13.3 min, p<0.001	Unsafe period: time when the clinician cannot visually distinguish amplitude of muscle twitches vs. use of quantitative monitoring to determine adequate respiratory recovery from NMB. No difference in clinical outcomes was reported.
Carron, et al. ¹⁹ R N=40 (20 in each group)	Pts having elective laparoscopic removal of adjustable gastric banding. ASA status I-III Suga 4 mg/kg TBW or Neo 70 mcg/kg (≤ 5 mg) of LBW+atropine 10 mcg/kg (≤ 1 mg) were given at 1-5 posttetanic counts after surgery and stopping rocur (<i>Profound NMB</i>)	Difference in anesthesia time between groups. Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle.	<u>Mean anesthesia time:</u> Suga: 47.9 min Neo: 95 min, p<0.0001 (Explained by the longer time to reach TOF=0.9 in Neo vs. Suga) <u>Mean reversal time:</u> Suga: 3.1 min Neo: 48.6 min, p<0.0001 <u>Mean time to extubation:</u> Suga: 8.6 min Neo: 9.85 min, p=0.08	All Suga pts achieved TOF=0.9 within 6 min while 75% of Neo recovered 30-60 min after reversal. Pts in Suga were able to swallow more quickly after extubation vs. Neo (7.1 vs. 12.2 min, respectively, p=0.003) and were able to get into bed quicker (24 min Suga vs. 33 min Neo, p=0.02.) No difference in pain, rescue drugs for pain but Neo had a higher PONV score vs. Suga (3.2 vs. 1.9, respectively on VAS p=0.015)
Gaszynski, et al. ²⁰ R, blinded PACU investigator N=70 (35 in each	Morbidly obese (BMI ≥ 40) Suga 2 mg/kg or Neo	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP	<u>Mean time to reach TOF=0.9:</u> Suga: 2 min Neo: 9 min, p<0.05	Two Suga pts reported strange taste in mouth while 3 Neo cases required added atropine

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group)	0.05 mg/kg ⁻¹ +atropine 0.02 mg/kg ⁻¹ CBW upon reappearance of T ₂ CBW=IBW+0.4(TBW- IBW)	muscle.		for significant bradycardia.
Geldner, et al. ²¹ R, blinded safety assessor N=140 (70 in each group)	ASA status I-III (85-93% ASA I-II) Suga 4 mg/kg given at 1-2 posttetanic counts (deep NMB) or Neo 50 mcg/kg+atropine 10 mcg/kg at reappearance of T ₂ (moderate NMB) after stopping rocur	Time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle.	<u>Mean time to reach TOF=0.9:</u> Suga: 2.4 min Neo: 8.4 min, p<0.0001 94% Suga vs. 20% Neo recovered from NMB in 5 min. <u>Geometric mean time from the last dose of rocur to reach TOF=0.9:</u> Suga: 13.3 min Neo: 35.2 min, p<0.0001 <u>OR Admit to D/C from OR:</u> Suga: 154 min Neo: 165 min, p=0.12 <u>Admin of drug to tracheal extubation:</u> Suga: 14 min Neo: 21 min, p<0.0001 <u>Admin of drug to OR discharge ready:</u> Suga: 15 min Neo: 21 min, p<0.0001 <u>Admin to PACU to D/C from PACU:</u> Suga: 20 min Neo: 24 min, p=0.46	Time to extubation and readiness for discharge from the OR was quicker with Suga vs, Neo by about a mean of 7 mi; the time from PACU admission to discharge from PACU was not different. 11% Suga and Neo 24% (bradycardia) reported ADEs that may have been related to study drug. No reoccurrence of NMB or residual NMB was noted except a suggestion of reoccurrence in one Suga pt, which last 45 min. <i>Authors concluded that earlier extubation and discharge from OR to PACU did not translate into more rapid discharge.</i>
Wu, et al. ²² R, blinded safety assessor N=Chinese 230 (Suga 119, Neo 111) N=Causasian 59 (Suga 29, Neo 30)	ASA Status I-III Suga 2mg/kg or Neo 50 mcg/kg+ atropine 10-20 mcg/kg were given at reappearance of T ₂ after stopping rocur (ABW used)	Mean time to reach TOF=0.9 <u>Monitoring:</u> Acceleromyograph AP muscle.	<u>Mean time to reach TOF=0.9: Chinese:</u> Suga: 1.6 min Neo: 9.1 min, p<0.0001 <u>Mean time to reach TOF=0.9: Causasian:</u> Suga: 1.4 min Neo: 6.7 min, p<0.0001	Higher incidence of ADEs (bradycardia and hypotension) in Neo vs. Suga. Authors concluded: Recovery of NMB with Suga was more rapid vs. Neo in both Chinese and Caucasian pts. No mention of clinical outcomes.
Lee, et al. ²³ R, blinded safety assessor N=115 (Rocur-Suga 57, SC 58)	ASA status I-II, mostly II Rocur 1.2 mg/kg followed in 3 min by Suga 16 mg/kg OR spontaneous recovery after SC 1 mg/kg to T ₁	Time to start of rocur or SC to recovery of T ₁ to 10% of baseline <u>Monitoring:</u> Acceleromyograph AP muscle.	<u>Time to start of rocur or SC to recovery of T₁ to 10% of baseline:</u> Suga: 4.4 min SC: 7.1 min, p<0.001 <u>Time to start of rocur or SC to recovery of T₁ to 90% of baseline:</u> Suga: 6.2 min SC: 10.9 min, p<0.001	Clinical signs of recovery were similar between groups, 50% of pts were awake and oriented prior to transfer to recovery and >90% at discharge from recovery. No signs of muscle weakness, etc. after extubation.
Sorensen, et al. ²⁴	Pts undergoing RSI,	Median time to correct	55 evaluated	Intubation conditions

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R, blinded pt and observer N=57 (Suga 30, SC 27)	ASA status I-III (92-93% ASA status I-II) Rocur 1 mg/kg or SC 1 mg/kg. Following intubation, Suga 16 mg/kg was administered in the rocur group.	placement of the tracheal tube to spontaneous ventilation (8 breaths/min and a tidal volume of at least 3ml/kg for 30 sec. <u>Monitoring:</u> Acceleromyograph AP muscle.	<u>Median time to correct placement of the tracheal tube to spontaneous ventilation:</u> Suga: 216 sec (3.6 min) SC: 406 sec (6.7 min), p=0.002 <u>Time from intubation to T₁=90%:</u> Suga: 168 sec (2.8 min) SC: 518 sec (8.6 min), p<0.0001 <u>Time from NMB admin to T₁=90%:</u> Suga: 282 sec (4.7 min) SC: 719 sec (11.9 min), p<0.0001	and time to tracheal intubation were not different between groups. SC: desaturation to 80% and bronchospasm each occurred in 1 pt and 2 with severe generalized muscle weakness. Suga: 3 pts experienced tachycardia with heart rates >100 beats/min
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A=atropine, ABW=actual body weight, ADE=adverse drug event, AP=adductor pollicis, BMI=body mass index, CBW=corrected body weight, Edro=edrophonium, Gly=glycopyrrolate, IBW=ideal body weight, LBW=lean body weight, Neo=neostigmine, OL=open label, PONV=postoperative nausea and vomiting, R=randomized, rocur=rocuronium. RSI=rapid sequence intubation, SC=succinylcholine, Suga=sugammadex, T₁=one twitch, T₂=two twitches, TBW=total body weight, TOF=train of four, VAS=visual analogue scale, vecur=vecuronium

ASA status: American Society of Anesthesiologists Health Status of Patient: ASA I=healthy, ASA II=mild disease, ASA III=severe systemic disease <https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system#>

There are a number of studies that evaluated the time to reversal of NMB with sugammadex in special populations. In general, sugammadex reversed NMB from rocuronium in less than 3 minutes and was well tolerated in patients with cardiac or pulmonary disease, in patients with severe or end-stage renal disease and in older patients. Additionally, sugammadex performed similarly in the presence of magnesium sulfate, antibiotics known to interfere with NMB agents and regardless of the general anesthetic agent used (propofol or sevoflurane). (See table 2 for details.)

Table 2: Reversal of Neuromuscular Blockade (Rocuronium) with Sugammadex in Special Populations

Trials	Characteristic of Population or Setting	Results (Efficacy and/or Safety)
Dahl, et al. N=116³²	Pts with NYHA II and III and ASA class II-IV undergoing noncardiac surgery	<u>Time to TOF=0.9:</u> Suga 2 mg/kg: 1.7 min Suga 4 mg/kg: 1.4 min Placebo: 34.3 min QTc vs. Placebo (NS) Heart rate was reduced and blood pressure increased 30 min after Suga vs. placebo but normalized post-anesthesia
Filho, et al. N=73³³ Czarnetzki, et al. N=32³⁴	Effectiveness of Suga 2 mg/kg in the presence of magnesium sulphate/sulfate	<u>Time to TOF=0.9</u> Suga+Mag: 1.91 min Suga: 2 min (NS) Suga+Mag: 1.69 min (moderate block) 1.77 min (Deep) Suga: 1.76 min (moderate block) 1.98 min (Deep) (NS)
Rex, et al. N=52³⁵ Suga 4 mg/kg Vanacker, et al. N=42 Suga 2 mg/kg³⁶	Effectiveness of Suga in pts under maintenance anesthesia with propofol or sevoflurane.	<u>Time to TOF=0.9</u> Propofol: 1.2 min Sevoflurane: 1.3 min (NS) Propofol: 1.8 min In Rex, no diff. in safety between anesthetics with Suga Sevoflurane: 1.8 min (NS) In Vanacker, QTc was statistically prolonged in the sevoflurane vs. propofol groups.
Staals, et al. N=30³⁷	Effectiveness and safety of Suga 2 mg/kg in patients with end-stage renal disease	<u>Time to TOF=0.9:</u> Renal disease: 2 min

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	(creatinine clearance <30 m/min) vs. healthy patients. Monitored for 48 hrs	Healthy: 1.65 min (NS) No residual or reoccurrence of NMB was observed
Hudson, et al.³⁸ N=197	Efficacy of Suga 4 mg/kg in patients receiving antibiotics that may interfere with NMB agents (kanamycin, gentamicin, vancomycin, clindamycin and bacitracin)	<u>Time to TOF=0.9:</u> Antibiotics: 1.6 min No Antibiotics: 2 min (NS)
Lee, et al. N=60³⁹	Efficacy of Suga 4 mg/kg in pts with mild hypothermia (34.5-35°C~95°F)	<u>Time to TOF=0.9:</u> Hypothermia: 2.85 min Normothermia: 2.1 min (p=0.005)
McDonagh, et al.⁴⁰ N=150	Efficacy of Suga 2 mg/kg in pts 18-64 years vs. 65 to >75 years.	<u>Time to TOF=0.9:</u> Adults: 2.3 min Elderly/Older elderly: 2.7 min (p=0.022)
Ulke, et al. N=10⁴¹	Efficacy of Suga 2 mg/kg in pts with myasthenia gravis undergoing thymectomy.	<u>Time to TOF=0.9:</u> 1.85 min
Amao, et al. N=77⁴²	Efficacy and safety of Suga 2 and 4 mg/kg in pts with pulmonary disease (Asthma or COPD) and ASA status II-III.	<u>Time to TOF=0.9:</u> Suga 2 mg/kg: 2.1 min Suga 4 mg/kg: 1.8 min 2/7 serious ADEs (bronchospasm) were felt to be possibly related to Suga.

ADEs=adverse drug events, ASA status: American Society of Anesthesiologists Health Status of Patient, COPD=chronic obstructive pulmonary disease, MAG=magnesium, NMB=neuromuscular block, NYHA=New York Heart Association Classification of Congestive Heart Failure, QTc=QT corrected, TOF=train of four=0.9 correlates with recovery of upper airway muscles and resolution of NMB.

Summary of Efficacy:

*Note: sugammadex should not be administered to reverse NMB caused by benzylisoquinolinium agents (e.g., atracurium and cisatracurium) since it is not effective for reversing NMB induced by these agents.

Comparison between sugammadex and neostigmine or edrophonium (Table 1):

- There are ten trials comparing the time to achieve pharyngeal and respiratory muscle recovery as assessed by quantitative monitoring of the adductor pollicis (thumb) muscle and reaching a train of four (TOF) \geq 0.9; which is considered to be near full neuromuscular recovery between sugammadex and neostigmine or edrophonium.
- In the trials, patients were generally younger and relatively healthy with a mean age of 50 years or less and American Society of Anesthesiologists (ASA) health status of I-II (healthy to mild systemic disease) in most trials.
- Time to achieve near full recovery to the point where reoccurrence of NMB or residual NMB is unlikely (TOF=0.9) was less than 3 to 5 minutes for sugammadex in most patients and ranged from less than 10 minutes to up to 50 minutes for neostigmine.
- Although the trials were not designed to identify differences in clinical outcomes, outcomes in the post-anesthesia care unit (PACU) and beyond were recorded. There were no clear consistent differences between sugammadex and neostigmine in terms of being awake, alert and oriented, ability to perform muscle related tasks such as 5 second head lift, or consequences of residual NMB after reversal.
 - In the study by Carron, et al. in 40 morbidly obese patients, mean time to tracheal extubation did not differ (Suga 8.6 vs. Neo 9.85 min, p=0.08) but ability to swallow after extubation occurred more quickly with sugammadex vs. neostigmine (7.1 vs. 12.2 min, respectively, p=0.003), ability to get into bed independently was faster with sugammadex vs. neostigmine (24 vs. 33 min, respectively, p=0.02), and time in PACU was less with sugammadex vs. neostigmine (37 vs. 48 min, respectively, p=0.01).¹⁹
 - In a study by Geldner, et al. in 140 patients with various levels of NMB undergoing laparoscopic surgery, time from admission to the operating room (OR) to discharge ready did not differ between sugammadex and neostigmine nor did the time from admission to the PACU to being considered ready for discharge from the PACU. However, time from drug administration to tracheal extubation and time from drug administration to being ready to discharge from the OR was shorter in the sugammadex vs. neostigmine groups (mean treatment difference between groups was approximately 6 and 6.5 minutes).²¹ In this study, the authors concluded that they were not able to show a difference in overall

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duration of time spent in the OR or the PACU. And, earlier tracheal extubation did not translate into more rapid discharge, but there may have been other factors preventing a difference in this outcome.

- Residual NMB was shown to be reduced when quantitative monitoring of reversal or recovery from NMB with acceleromyography was used compared to qualitative monitoring.
 - Baillard, et al., prospectively enrolled surgical patients during three separate time periods (1995, 2000, 2004). Between 1995 and 2004, the use of quantitative monitoring and reversal agents became increasingly more common. The authors report that incomplete NMB reversal decreased from 62% in 1995 to 3.5% in 2004, attributing this reduction to use of quantitative monitoring and use of NMB reversal agents. No effect on outcomes were reported.²⁵
 - The risk for residual NMB was shown to be higher when qualitative monitoring was compared to quantitative monitoring using acceleromyography (50% vs. 14.5%, respectively p<0.0001) for recovery but clinical signs of muscle weakness were small and did not differ between groups.⁷
 - In a prospective, propensity score matched cohort study, 18,579 surgical patients receiving NMB agents were matched with 18,579 patients that did not receive NMB drugs.²⁶ The primary outcome of oxygen desaturation after tracheal extubation (defined as: oxygen saturation <90% with a decrease in oxygen saturation of >3%) and the need for reintubation was compared in patients who received and who did not receive NMB agents. The effect of using qualitative monitoring for recovery from NMB and use of neostigmine as a reversal agent on oxygen saturation were also examined. The use of NMB agents increased the risk for oxygen desaturation after extubation (OR 1.36, 95% CI 1.23-1.51) and reintubation that required admission to an intensive care unit (OR 1.4, 95% CI 1.09-1.80). The use of qualitative monitoring did not reduce the risk for oxygen desaturation (OR 1.19, 95% CI 1.07-1.32) or reintubation (OR 1.49, 95% CI 1.16-1.90) and reversal with neostigmine did not reduce risk for desaturation (OR 1.32, 95% CI 1.2-1.46) or the need for reintubation within seven days of surgery (OR 1.76, 95% CI 1.38-2.26).
 - Todd, et al., reported implementation of a program involving quantitative monitoring over a two-year period which showed a rate of 2-4 re-intubations/year in the PACU prior to implementation vs. no reported re-intubations in the PACU in the two years since implementation. Neostigmine was used for reversing NMB.²⁷
 - Todd, et al., reported in a letter to the editor some follow-up information and included two cases of residual or reoccurrence of NMB reversal since implementation of quantitative monitoring. A review of these two cases revealed that neither case was properly monitoring for NMB reversal. The authors reinforce that since implementation of their educational program regarding the importance of quantitative monitoring and availability of equipment to conduct this type of monitoring, there have been no cases of re-intubation in properly monitored patients.²⁸
- Effect of incomplete reversal of NMB or residual NMB on outcomes:
 - Sauer, et al., conducted a study in patients having orthopedic surgery in which they were randomized to neostigmine 20mcg/kg or placebo and measured hypoxemia (oxygen saturation of <93%). Using quantitative and qualitative monitoring, once the TOF=1 was reached in the neostigmine group, the tracheal tube was removed. In the placebo group, the tube was removed once patients exhibited TOF <1 but without fade in TOF and double-burst stimulation. A higher number of patients not receiving a reversal agent developed hypoxemia vs. those that received neostigmine (29 vs. 16, p=0.021).²⁹
 - In a large prospective cohort study, the use of intermediate acting NMB agents increased the risk for oxygen desaturation <90% after tracheal extubation as well as increased the risk for reintubation. The use of qualitative monitoring and reversal with neostigmine also increased the risk for these postoperative events.²⁶
 - In an invited commentary, the author briefly comments on a number of related articles but notes that “Whether the way that NMB is managed can affect the postoperative pulmonary outcome is the missing piece of the puzzle” and findings from retrospective or non-randomized studies should be confirmed in properly designed and powered prospective, randomized trials.³⁰
- Special populations at risk for residual NMB: (Older age and ASA status of 3 and 4)

- In a retrospective data analysis of 1444 patients undergoing surgery and receiving NMB agents, 722 were reversed with sugammadex and 722 with neostigmine or no reversal agent. Oxygen saturation while in PACU and upon discharge from the PACU, length of stay in PACU and hospital stay were not different between sugammadex and neostigmine/no reversal agent groups. In terms of pulmonary outcomes, which included chest radiographs, pulmonary symptoms and physical exam, no differences were noted between groups for these individual parameters. However, it was noted that “the pulmonary outcome score” was higher in the neostigmine/no reversal agent vs. sugammadex. Authors note that the pulmonary outcome score has not been validated but appears to be significantly influenced by age and ASA status. The use of neostigmine or no reversal agent did not improve these scores but use of sugammadex seemed to blunt the influence of age and ASA status 3/4 on pulmonary outcomes. Authors concluded that they observed a lower risk for adverse pulmonary outcomes in older patients with an ASA status of 3 or 4 (severe systemic disease or severe systemic disease that is a constant threat to life) who were given sugammadex to reverse NMB versus no effect on pulmonary outcomes when neostigmine was used to reverse NMB vs. no reversal. However, authors also note that they did not find differences between sugammadex and neostigmine in airway competency or length of stay in the PACU or hospital. They note limitations of their study including retrospective design, heterogeneous population, combining neostigmine with no reversal agent as a single group, pulmonary outcome score had not been validated, authors were unable to determine how recovery from NMB was monitored, etc.³¹
- In a prospective cohort-matched observational study, the incidence of postoperative residual NMB (PRNB) was compared between an elderly (N=150, 70-90 year) and younger cohort (N=150, 18-50 years) of patients. The incidence of PRNB (TOF<0.9) was higher in the older vs. younger cohort (57.7% vs. 30%, p<0.001). More elderly patients developed airway obstruction on their way to the PACU vs. younger patients (18.8% vs. 7.3%, p=0.003). There was also a higher use of oxygen in the older group vs. younger, more symptoms of muscle weakness at PACU admission and 20 minutes later than in the younger cohort. Compared with the younger group, there was a higher incidence of pulmonary complications in the older group (2% vs. 15.4%, respectively, p<0.001) and a longer length of stay (0.25 days vs. 1.25 days, respectively, p<0.001).¹⁰ The authors acknowledge limitations of their study design, calibration of quantitative measuring devices was not done and it was not clear which muscle was used to measure recovery (eye muscle vs. thumb). The authors conclude that in light of their findings from this observational study, the use of quantitative monitoring or sugammadex is needed to ensure full recovery from NMB in elderly surgical patients.
- Additional studies are required to determine if use of sugammadex will result in improved outcomes after reversal in terms of neuromuscular function and consequences of residual or reoccurrence of NMB versus use of neostigmine. Additionally, if more widespread use of quantitative monitoring will reduce the risk of residual NMB with neostigmine or potentially sugammadex. Alternatively, if quantitative monitoring and reversal with neostigmine will result in similar outcomes vs. use of sugammadex for reversal with or without quantitative monitoring. Risk for residual block and potential for its consequences or complications may be higher in patients with the following conditions: morbid obesity, obstructive sleep apnea, cardiopulmonary disease, older patients and in those with overall poorer health status. In the two non-randomized studies in elderly patients or those with severe systemic disease (ASA 3 or 4), these patients may be candidates for sugammadex since they may be at greater risk for residual NMB and pulmonary complications but prospective evidence proving better outcomes with sugammadex vs. neostigmine is not yet available.

Comparison of need for rapid reversal vs. spontaneous recovery with succinylcholine (Table 1):

- There are two studies comparing the rapid reversal of NMB with sugammadex versus spontaneous recovery of NMB with succinylcholine.²³⁻²⁴
- The endpoints were different than time to achieve TOF= \geq 0.9 and included time to recover amplitude of first twitch to 10% of baseline and time to placement of tracheal tube to spontaneous ventilation. In both studies, sugammadex reached the primary endpoint more quickly than spontaneous reversal after succinylcholine (approximately 3-4 minutes more quickly). In both studies, sugammadex 16 mg/kg was used for rapid reversal of rocuronium.

Reversal of NMB with sugammadex vs. placebo in special populations or specific circumstances (Table 2).³²⁻⁴²

- In general, sugammadex reversed NMB from rocuronium in less than 3 minutes and was well tolerated in patients with cardiac or pulmonary disease, in patients with severe or end-stage renal disease and in older patients.
- Additionally, sugammadex performed similarly in the presence of magnesium sulfate, antibiotics known to interfere with NMB agents and regardless of the general anesthetic agent used (propofol or sevoflurane).
- There was a single published case report of sugammadex being used to reverse NMB in a patient who had emergency exploratory laparotomy after rapid sequence intubation with rocuronium. After surgery, neostigmine was administered but recovery was less than expected. Sugammadex was given and complete reversal was observed within 2 minutes.⁴³

Table 3.

	Neostigmine	Sugammadex
Dose	50-70 mcg/kg was used in trials In those trials, 50 mcg was used for reversing moderate block and 70 mcg was used for reducing greater degrees of block (But neostigmine should not be used for deep or profound block. In trials, patients recovered to 2 twitches (moderate block) before administration.	2, 4 or 16 mg/kg. Dose depends upon the degree of NMB. 2 mg/kg for moderate, 4 mg/kg for deep block and 16 mg/kg is reserved if there is a need for rapid reversal of rocuronium
Mean/Median time to reach TOF=0.9 or >*	3-5 min in most pts	<10 min to up to 50 min
Necessary concomitant meds	Glycopyrrolate or atropine	No
When to administer?	At appearance of T ₂ . Given when there are signs of recovery of NMB, at moderate block. It is not used for reversing deep or profound block	When recovery from NMB is desired, no need to wait for signs of recovery from NMB
Use in deep or profound NMB?	No	Yes
Need for quantitative monitoring	Yes	Yes?

*There were some patients that were delayed in reaching TOF 0.9 or > and exceeded the times listed above for both sugammadex and neostigmine. T₂=reappearance of second twitch, representing moderate block.

Potential Off-Label Use

- Potential to be used for reversing nondepolarizing neuromuscular blocking agents other than rocuronium or vecuronium.⁴⁴ The use of sugammadex for reversing neuromuscular block from agents other than rocuronium or vecuronium is not recommended.
- Sugammadex should not be administered to reverse NMB caused by benzylisoquinolinium agents (e.g., atracurium and cisatracurium) since it is not effective for reversing NMB induced by these agents.

Safety¹⁻²

(For more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • None
Contraindications	<ul style="list-style-type: none"> • Known hypersensitivity to sugammadex or any of its components
Warnings/Precautions	<p><u>Hypersensitivity/Anaphylaxis:</u> The severity of these reactions can vary from isolated skin reactions to serious systemic reactions (anaphylaxis and anaphylactic shock).</p> <ul style="list-style-type: none"> ○ Anaphylaxis has been reported in 0.3% of healthy volunteers. Patients should be monitored for an appropriate duration after administration of sugammadex. ○ Providers should be aware that in trials where anaphylaxis occurred,

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it was frequently associated with life-threatening cardiovascular events requiring immediate and aggressive management.

- Severe hypersensitivity reactions have occurred in patients with no prior exposure to sugammadex.
- Significant **bradycardia** has been reported within minutes of administration of sugammadex; some cases of which have resulted in cardiac arrest.
- Patients must be provided with ventilatory support until adequate spontaneous respiration has been restored and a patent airway is ensured. In the event that neuromuscular blockade persists or recurs following removal of ventilatory support, steps must be taken to provide sufficient ventilation.
- Recurrence of neuromuscular blockade was observed in <1% of patients following an appropriate dose of sugammadex for reversal of rocuronium or vecuronium.

Safety Considerations¹⁻²

- Sugammadex was submitted for approval in 2008 but was not approved for use in the United States since there were safety concerns associated with hypersensitivity reactions and anaphylaxis upon repeat exposure and a lack of information on the effect of sugammadex on clotting and perioperative bleeding.
 - The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) concluded that sugammadex can cause hypersensitivity reactions and anaphylaxis and the risk seems to increase with the use of higher doses. Repeated doses of sugammadex did not appear to increase the risk for or the severity of these reactions. The rate of hypersensitivity reactions with sugammadex compared to other drugs used in the operative setting is unclear. Therefore, a benefit-risk assessment must be made when determining use of sugammadex.
 - The Division of Hematology Products (DHP) concurred that in a study of patients undergoing orthopedic surgery of the lower limb and receiving heparin thromboprophylaxis, there was no evidence that sugammadex versus usual care (neostigmine) increased the frequency of hemorrhage despite some prolongation of aPTT and PT (lasting for under sixty minutes) after sugammadex administration. From the evidence reviewed, DHP concluded that the risk for postoperative bleeding after administration of sugammadex is not higher than that following neostigmine or spontaneous recovery from rocuronium or vecuronium.^{2,4,5}
 - Post-marketing reports of bleeding (July 2008-June 2012): Two of the reports occurred at the operative site and were not considered related to sugammadex. One patient developed disseminated intravascular coagulation (DIC) subsequent to anaphylaxis and bleeding was reported at multiple sites after gastrectomy. The patient died 3 days after surgery from multiple organ failure and cardiac arrest. Another patient experienced bradycardia with cardiac arrest within a minute of receiving sugammadex. An intra-aortic balloon pump was inserted and the patient developed intra-abdominal bleeding since the pump lacerated his aorta. The patient died 19 days later. The last case involved a patient having orthopedic surgery of the femur and was reported to develop hypotension, bradycardia and hemorrhagic shock later in the day after surgery.
- In a single trial and in post-marketing reports, bronchospasm was reported as being potentially related to sugammadex in patients with a history of pulmonary complications.

Adverse Reactions¹⁻²

Common adverse reactions	Adverse reactions reported by $\geq 10\%$ of patients and at a greater rate than placebo include vomiting, nausea, hypotension and headache. Adverse events do not appear to be dose-dependent with the exception of potentially anaphylaxis, hypersensitivity reactions and dysgeusia, which occurred at a higher frequency with the 16 mg/kg dose vs. the 2 or 4 mg/kg doses.
Death/Serious adverse reactions	There were a total of 8 deaths during the clinical development program, 4 in the sugammadex, 1 in the neostigmine and 3 in the placebo group. All deaths occurred after the study had been completed. The manufacturer states that all deaths were unrelated to sugammadex but the FDA reviewer felt that

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sugammadex may have contributed to one of the deaths. However, the single death was reported in the original submission from 2008 and since that time the number of patients exposed to sugammadex in the clinical development program has increased significantly with no further deaths related to sugammadex. The reviewer concluded that there are no additional evidence that sugammadex increases mortality.

From the FDA review of sugammadex, serious adverse events were reported in 48% placebo, 40% of sugammadex and 46% of patients receiving neostigmine.

Discontinuations due to adverse reactions

Since sugammadex is given as a single bolus injection, no patients discontinued treatment due to an adverse event in the trials reviewed by the FDA for approval. Instead, there were a number of patients who withdrew from the trial due to an adverse event. Overall, there were 75 patients that withdrew from trials: 50 treated with sugammadex, 23 treated with placebo and 1 treated with neostigmine. There did not appear to be dose-dependent adverse events that led to study withdrawal with sugammadex. Notable adverse events associated with discontinuation of sugammadex included: 1 for anaphylactic shock (16 mg/kg), 2 due to hypersensitivity reactions (4 mg/kg and 32 mg/kg) and 1 for tachycardia (8 mg/kg).

Drug Interactions

Drug-Drug Interactions

- Toremifene has a high binding affinity for sugammadex. Therefore, displacement of some rocuronium or vecuronium from the sugammadex-neuromuscular blocking agent complex may occur leading to a delay in reversing the neuromuscular block if toremifene is given on the same day of surgery.
- Based upon evidence from in vitro studies, sugammadex may bind to progestogen, which can reduce progestogen exposure. This binding can mimic the effect of missing a daily dose of an oral contraceptive. Therefore, if an oral contraceptive is taken on the day of surgery, the patient should be advised to use a second, non-hormonal contraceptive method or back-up method (e.g., condoms, spermicide, etc.) for the following 7 days. For non-oral hormonal contraceptives, the same advice applies.
- Drugs that can potentiate neuromuscular blockade and may delay reversal or increase the possibility that the neuromuscular block will reoccur.
 - Vecuronium: inhalational anesthetics (enflurane or isoflurane), certain antibiotics can produce neuromuscular block on their own or intensify the block (aminoglycosides, tetracyclines, bacitracin, streptomycin, polymyxin B, colistin and sodium colistimethate) and quinidine.
 - Rocuronium: inhalational anesthetics (enflurane or isoflurane), certain antibiotics can produce neuromuscular block on their own or intensify the block, quinidine, magnesium salts, lithium, local anesthetics, procainamide and quinidine.
 - Neuromuscular blockade can be altered by a number of factors including electrolyte imbalances, changes in acid/base status, etc.

Drug-Lab Interactions

- Sugammadex may interfere with the serum progesterone assay, which can be affected for up to 30 minutes after a 16 mg/kg dose.

Risk Evaluation

As of April 28, 2016

	Comments
Sentinel event advisories	<ul style="list-style-type: none"> • None
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> • Sugammadex 100 mg/ml: Suvorexant, Ryanodex • Bridion: Bupropion, Brevicon

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- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Post-marketing surveillance identified the following adverse events:

- Cardiac disorders including marked bradycardia and cardiac arrest associated with bradycardia occurred within minutes of sugammadex administration. Others reports of cardiac events include atrial fibrillation, atrioventricular (AV) block, cardiac/cardiorespiratory arrest, ST segment changes, supraventricular tachycardia/extrasystoles, tachycardia, ventricular fibrillation and ventricular tachycardia.
- Circumstances where sugammadex did not have the intended reversal effect.
- Reports of severe hypersensitivity including anaphylactic shock, anaphylactic and anaphylactoid reactions.
- Reported cases of laryngospasm, dyspnea, wheezing, pulmonary edema and respiratory arrest have occurred in association with sugammadex.
- Because these reports are voluntary, a causal relationship or frequency of occurrence is unknown.

There have been several retrospective, cost-effectiveness studies or reports⁴⁷⁻⁵¹; two of them found that sugammadex may be cost-effective if time saved is limited to the operating room. However, if time is saved in the recovery room, it was not considered to be cost-effective. In one study, use of sugammadex in higher risk patients (e.g., elderly, morbidly obese, neurologic, neuromuscular, respiratory, cardiac, kidney or liver impairment) was felt to be cost-effective.

Dosing and Administration

Sugammadex can be used to reverse various levels of neuromuscular blockade induced by rocuronium or vecuronium. The dose of sugammadex does not depend upon anesthetic regimen. *Note: sugammadex should not be administered to reverse NMB caused by benzylisoquinolinium agents (e.g., atracurium and cisatracurium) since it is not effective for reversing these agents. Additionally, under dosing should be avoided since it can lead to suboptimal reversal of NMB or reoccurrence of NMB.

DOSING: (Dosing is based upon actual body weight)

For neuromuscular block induced by rocuronium or vecuronium:

- 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation following rocuronium or vecuronium induced neuromuscular blockade.
- 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch (T₂) in response to TOF stimulation following rocuronium or vecuronium induced neuromuscular blockade.

For neuromuscular block induced by rocuronium:

- 16 mg/kg is recommended if there is a clinical need to reverse the neuromuscular blockade quickly (within 3 minutes) after administration of a single dose of rocuronium of 1.2 mg/kg. Evidence is not available for vecuronium in this setting.

ADMINISTRATION:

- Only those healthcare professionals that are trained in the use, actions, characteristics and complications of neuromuscular blocking drugs and reversal agents should administer sugammadex.
- Dosage and timing of sugammadex ultimately depends upon monitoring for twitch responses and the extent of spontaneous recovery that has taken place.
- Sugammadex is administered as a single intravenous bolus given over ten seconds into an existing line.
- Patients should be monitored from the time sugammadex is administered until complete recovery of neuromuscular function to ensure the patient maintains adequate ventilation and a patent airway. Satisfactory recovery is assessed through skeletal muscle tone and respiratory measurements in addition to response to peripheral nerve stimulation.

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COMPATABILITY:

- Sugammadex may be injected into an intravenous line with the following:
 - 0.9% Sodium Chloride
 - 5% Dextrose
 - 0.45% Sodium Chloride and 2.5% Dextrose
 - 5% Dextrose in 0.9% Sodium Chloride
 - Isolyte P with 5% Dextrose
 - Ringer's Lactate Solution
 - Ringer's Solution
- The intravenous line should be flushed between administration of sugammadex and other medications.
- Sugammadex is not compatible with verapamil, ondansetron or ranitidine.

WAITING TIMES FOR RE-ADMINISTERING NMB AGENTS:

MINIMUM WAITING PERIOD	NMB DRUG AND DOSE to be ADMINISTERED
5 minutes	1.2 mg/kg rocuronium
4 hours	0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium
24 hours (mild to moderate renal impairment)	0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after reversal with up to 4 mg/kg sugammadex. If a shorter waiting period is needed, give rocuronium 1.2 mg/kg
24 hours (after 16 mg/kg sugammadex)	---
If NMB is required before recommended waiting time has passed.	Use nonsteroidal NMB drug (e.g. atracurium or cisatracurium)

If rocuronium 1.2 mg/kg is administered within 30 minutes of reversal with sugammadex, time to NMB may be delayed up to 4 minutes and duration of effect may be shorter by about 15 minutes.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • Available evidence does not support the need for a dosage adjustment in elderly patients. However, since sugammadex is primarily renally excreted, the risk for adverse events may be increased in elderly patients since they are more likely to have some degree of renal impairment. Therefore, care must be taken in selection of the proper dose and renal function should be monitored.
Pregnancy	<ul style="list-style-type: none"> • There are no data in pregnant humans so the risk/benefit to the fetus must be weighed against the need to use sugammadex. There are no specific recommendations provided in the manufacturer labeling.
Lactation	<ul style="list-style-type: none"> • No data available. The developmental and health benefits of breastfeeding must be weighed against the nursing mothers need for sugammadex and the possibility for adverse events on the infant from sugammadex use and from the mothers underlying condition.
Renal Impairment	<ul style="list-style-type: none"> • Primarily, the kidneys excrete Sugammadex. In a study of older patients with mild to moderate renal insufficiency, clearance of sugammadex was reduced but no difference was seen in the ability of sugammadex to reverse neuromuscular blockade of rocuronium. As a result, no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment, sugammadex is not recommended for use because of the lack of evidence in these patients and the potential for prolonged and increased exposure of these patients to sugammadex. • In a pharmacokinetic study of 15 pts with severe to end stage renal disease (creatinine clearance <30 ml/min) compared to healthy controls, clearance of sugammadex was significantly reduced and

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	half-life significantly prolonged in pts with renal disease. ⁴⁶ In another study by Staals, et al., time to reversal of NMB was similar in severe renal impairment vs. healthy controls with no serious adverse events related to sugammadex. ³⁷
Hepatic Impairment	<ul style="list-style-type: none"> No trials have been conducted in patients with liver impairment since sugammadex is not metabolized or eliminated from the body by the liver. Caution is advised when using sugammadex in a patient with liver impairment and coagulopathy or marked edema.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> No data identified.
Cardiac Conditions	<ul style="list-style-type: none"> In a trial of 76 patients with a history of heart disease including ischemic heart disease, heart failure [primarily New York Heart Association II] or arrhythmias, recovery times from neuromuscular blockade was similar to other trials and therefore, no dosage adjustment is necessary.
Pulmonary Conditions	<ul style="list-style-type: none"> In a trial of 77 patients with a history of pulmonary disease or complications, recovery times from neuromuscular blockage was similar to other trials and therefore, no dosage adjustment is necessary.

Projected Place in Therapy

- It is estimated that general anesthesia is used in up to 50 million surgical patients annually in the United States and more than one-third of those patients will receive a NMB agent.⁵² A significant proportion of patients receiving NMB agents will require reversal after their surgery has been completed. The decision to reverse neuromuscular blockade is complex and ultimately is left to the discretion of the anesthesiologist but may be dependent upon a number of factors including the patients level of NMB and time to completion of the procedure, duration of surgery, if the patient has already begun to spontaneously recover, etc.⁵³
- Historically, the standard reversal agent has been neostigmine combined with glycopyrrolate or atropine to counteract the cholinergic side effects. In December 2015, sugammadex (Bridion®) was approved for reversing NMB caused by rocuronium or vecuronium.
- Sugammadex works differently than acetylcholinestase inhibitors (e.g., neostigmine, edrophonium) in that it encapsulates the NMB agent and more rapidly reverses the NMB when compared to neostigmine. At this time, prospective evidence is not available that supports an improvement in post-operative outcomes between sugammadex and neostigmine.
- Additionally, it is increasingly recognized that recovery from NMB agents should be monitored using quantitative, objective monitoring as opposed to qualitative monitoring. The risk for residual NMB is lower when patients are quantitatively monitored. It is unclear whether use of sugammadex vs. neostigmine for NMB reversal will result in improved respiratory or other outcomes or consistently reduce time in the operating room. Additionally, whether use of quantitative monitoring of neostigmine reversal will result in different outcomes compared to reversal with sugammadex with or without quantitative monitoring of recovery from NMB is unknown.
- There have been several retrospective, cost-effectiveness studies or reports; two of which found that sugammadex may be cost-effective if time saved is limited to the operating room. However, if time is saved in the recovery room, it was not considered to be cost-effective. In one study, use of sugammadex in higher risk patients (e.g., elderly, morbidly obese, neurologic, neuromuscular, respiratory, cardiac, kidney or liver impairment) was felt to be cost-effective.
- A letter from the American Society of Anesthesiologists to the Anesthetic and Analgesic Drug Products Advisory Committee in 2013 indicated their interest in the use of sugammadex, especially in those patients considered to be at the highest risk (e.g., emphysema, obstructive sleep apnea, myasthenia gravis, morbid obesity, advanced age, etc.).
- Sugammadex reduces NMB more quickly than neostigmine but prospective evidence is lacking to support an improvement in respiratory or other outcomes when used routinely over neostigmine. However, the risk for residual or reoccurrence of NMB may be increased in certain higher risk patients (advanced age, ASA status 3 or 4, morbid obesity, obstructive sleep apnea, reduced pulmonary reserve and overall poorer health), especially

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when quantitative monitoring is not utilized routinely, and therefore the use of sugammadex may be appropriate in selected high-risk individuals. Additionally, the use of sugammadex may be appropriate when surgical cases necessitate deep NMB throughout the duration of the procedure and rapid reversal is needed or when use of succinylcholine should be avoided (e.g., Trauma, prolonged immobilization (up-regulation of nicotinic receptors), muscular dystrophies, severe burns (>48 hours after burn), crush injury, renal failure, polyneuropathies, etc. (Settings in which admin. can lead to hyperkalemia). **As a result, until more clinical data are available, it would be prudent to reserve this agent for patients in whom a higher risk for residual NMB and its complications are expected, or for patients where succinylcholine should be avoided, as follows:**

- **Conditions in which patients may be at higher risk for residual NMB and its complications where sugammadex may be preferred over neostigmine:** Morbid obesity, obstructive sleep apnea, advanced age, poorer health status (ASA physical status of 3 or 4), impaired pulmonary function, need for deep neuromuscular block throughout operative procedure, surgeries ending abruptly or sooner than expected, cannot-intubate, cannot-ventilate settings, etc.
- **Conditions in which patients may be at higher risk for severe hyperkalemia or malignant hyperthermia where succinylcholine should be avoided for RSI:** Trauma, prolonged immobilization, neuromuscular disorders, >48 hours after severe burns, crush injuries, renal failure, etc.

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PHARMACOECONOMIC STUDIES

Study	Study Details
<p>Ledowski 2012⁴⁷ Retrospective audit (Single site)</p>	<ul style="list-style-type: none"> • Unrestricted use of sugammadex for reversing amino-steroidal NMB • Data collected for one month in all intubated patients in 2010 and again in 2011 to compare NMB usage and associated costs • Use of sugammadex increased by 743% • Use of neostigmine/glycopyrrolate was reduced by 48% • 2010: Associated cost of NMB was \$8,913 and reversal was \$9,622 equaling about \$42 per case and \$0.27 per minute of anesthesia. • 2011: Associated cost of NMB was \$9,494 and reversal increased significantly to \$48,907 equaling about \$127 per case and \$0.88 per minute of anesthesia. • Time in surgery, anesthesia and PACU did not differ between 2010 and 2011 • Hospital stay was reduced 5 hrs from 2010 to 2011 (78 hours vs. 73 hours, respectively. P=0.044) and surgery to hospital discharge was reduced 0.2 days from 2010 to 2011 (2.2 vs. 2 days, respectively. P=0.01) • Use of atracurium (from 180 to 40) and cis-atracurium (from 170-95) were reduced significantly and use of rocuronium (from 550-700) and vecuronium (from 30-50) increased. • Authors state that no conclusions can be drawn from the audit but represents an observation that is worth further study.
<p>Fuchs-Buder 2012⁴⁸ Review</p>	<ul style="list-style-type: none"> • From evidence reviewed, authors suggest that sugammadex may have potential to reduce recovery times. • However, reducing anesthesia time alone does not translate into added resources for scheduled operations and that for sugammadex to reduce real costs, the workflow process as well as the anesthesia time need to be optimized.
<p>Health Tech Assessment 2010⁴⁹ Systematic review/cost-effective in UK</p>	<ul style="list-style-type: none"> • Authors state that their economic assessment was severely limited by the lack of evidence needed for many of the parameters. • Considered two scenarios: 1) routine induction and reversal of NMB, 2) rapid induction and/or reversal of NMB. • Sugammadex appeared to be cost-effective for routine reversal of NMB if <u>all reductions in time are achieved in the operating room</u>. It is not cost-effective <u>if reductions in recovery time are obtained in the recovery room</u>. • For rapid induction and reversal (urgent or emergent setting), the reduction in morbidity was not likely to save costs when comparing use of sugammadex to succinylcholine.
<p>Paton 2010⁵⁰ Review</p>	<ul style="list-style-type: none"> • From three trials reviewed and considering “value of time saved” in patients with moderate NMB, use of sugammadex would be <u>cost-effective if the time was saved in the operating room</u>. • It would <u>not be cost-effective if the time were saved in the recovery room</u>. • Authors state that there is uncertainty in these results and conclude that sugammadex may be cost-effective if the time saved in the operating room can be put to productive use in practice. • Authors call for additional research for sugammadex with regard to patient safety, predictable recovery from NMB, outcomes and economic use of resources.

<p>Carron 2016⁵¹ Retrospective (single site) Italian study</p>	<ul style="list-style-type: none"> • Sugammadex as first choice reversal agent or as rescue treatment after neostigmine vs. control (matched controls receiving neostigmine and not sugammadex) • Two periods were compared: 2011-12 and 2013-14 • Those patients judged to have an increased risk of complications with reversal by neostigmine were given sugammadex for reversal and termed “preventive use.” <i>These patients included: elderly, morbid obesity, neurologic, neuromuscular, respiratory, cardiac, kidney or liver impairment, those with difficult airway or with contraindications to neostigmine plus atropine.</i> • Rescue use was defined as “emergency use” and included those that could not be intubated (cannot ventilate or intubate) or curative after reversal with neostigmine and TOF >0.9 not reached. • Preventative use represented 3% of all cases. Control group had more patients with mild-moderate NMB at extubation, even some with severe block. Stay in recovery was longer in control. There were 10 unplanned ICU admissions during 2011-12 and one in 2013-14. • Curative use of sugammadex represented 3.2% of cases. Higher number of severe residual NMB and mild-moderate block when sugammadex was used as rescue therapy due to adverse respiratory events vs. control. Length of stay in recovery did not differ between groups. No unplanned ICU admissions were observed in the rescue or curative group vs. control. • Authors conclude that when sugammadex was used as preventative treatment in high-risk patients with quantitative monitoring, TOF indicating full recovery was reached in all patients and they were discharged more quickly to surgical ward. Felt to be cost-effective. • When used as curative therapy after adverse respiratory events were observed after reversal with neostigmine, no difference in time to discharge to surgical ward was observed. Also, no unplanned ICU admissions were observed. • Authors conclude the potential to avoid an ICU related admissions due to residual NMB is cost-effective. Sugammadex was used as a first choice in higher risk patients (see above).
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