Sugammadex
A Review of its Use in Anaesthetic Practice

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Data Selection
Sources: Medical literature published in any language since 1980 on ‘sugammadex’, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were ‘sugammadex’ or ‘ORG-25969’. Searches were last updated 7 May 2009.

Selection: Studies in patients undergoing surgery who received sugammadex. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Sugammadex, selective relaxant binding agent, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Sugammadex (Bridion®), a modified γ-cyclodextrin, is the first selective relaxant binding agent indicated to reverse the neuromuscular blockade induced during general anaesthesia to facilitate surgical procedures. The mechanism of action of sugammadex differs from that of other commonly used reversal agents, such as neostigmine and edrophonium. In the EU, sugammadex is recommended for use in the reversal of rocuronium- or vecuronium-induced moderate or deep muscle relaxation in adult (including elderly) patients and reversal of rocuronium-induced moderate muscle relaxation in paediatric patients (aged 2–17 years). Sugammadex is also approved in Australia, Iceland, New Zealand and Norway.

In clinical trials in adult surgical patients with relatively good health, sugammadex at recommended doses provided rapid reversal of rocuronium- or vecuronium-induced neuromuscular blockade with a low incidence of residual or recurrent neuromuscular blockade and was generally well tolerated. In paediatric patients, sugammadex effectively reversed rocuronium-induced neuromuscular blockade and was generally well tolerated. Several factors associated with the use of sugammadex have yet to be determined, such as the efficacy and safety in patients with poorer health or in those with neuromuscular disorders, the incidence of infrequent adverse events in larger patient populations and the cost effectiveness of the drug relative to existing reversal agents. Nevertheless, sugammadex is a useful addition to the reversal agents commonly employed in anaesthetic practice.

Pharmacological Properties

Sugammadex encapsulates and inactivates rocuronium; it selectively binds to free rocuronium molecules with high affinity at a molar ratio of 1:1. The resulting inactive complex is eliminated from the body according to the pharmacokinetic properties of sugammadex. Sugammadex also has high affinity for vecuronium. In several phase I and II trials, sugammadex demonstrated dose-dependent reversal of rocuronium- or vecuronium-induced blockade when administered at the reappearance of the second twitch of the train-of-four stimulation (T2) or at a post-tetanic count of 1–2 (1–2 PTC), or 3–15 minutes after the administration of the neuromuscular blocking agent. Sugammadex has no clinically relevant effects on the cardiovascular and haemodynamic systems (including corrected QT interval prolongation).

Intravenous sugammadex demonstrates linear pharmacokinetic properties over the dose range of 1–16 mg/kg. The steady-state volume of distribution after a single dose is =11–14 L. Sugammadex and the sugammadex-rocuronium complex do not bind to plasma proteins or erythrocytes. Sugammadex does not appear to undergo metabolism and is primarily excreted in the urine as unchanged drug; the elimination half-life is 1.8 hours. Administration of sugammadex following that of rocuronium increases the plasma concentration of rocuronium (in a manner dependent on the dose of sugammadex), shortens its elimination half-life (by ≈30%) and increases the urinary excretion (by 2- to 3-fold) of rocuronium; however, these changes are not associated with an increase in the level of neuro-
muscular blockade. Unlike rocuronium, the sugammadex-rocuronium complex is not eliminated via the biliary route. Renal impairment (but not hepatic impairment or patient age) delays the elimination of sugammadex and the sugammadex-rocuronium complex, and the use of sugammadex in patients with severe renal impairment is not recommended.

**Therapeutic Efficacy**

The efficacy of sugammadex has been evaluated in several well designed phase III trials in adult (including elderly) or paediatric surgical patients. In adult patients, sugammadex 2 mg/kg reversed rocuronium 0.6 mg/kg or vecuronium 0.1 mg/kg significantly faster than neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg, when administered at the reappearance of T2. In addition, the reversal of rocuronium 0.6 mg/kg by sugammadex 2 mg/kg was significantly faster than the reversal of cisatracurium 0.15 mg/kg by neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg. Sugammadex 4 mg/kg reversed rocuronium 0.6 mg/kg or vecuronium 0.1 mg/kg significantly faster than neostigmine 70 µg/kg plus glycopyrrolate 14 µg/kg, when administered at 1–2 PTC. When administered 3 minutes after rocuronium, sugammadex 16 mg/kg reversed rocuronium 1.2 mg/kg significantly faster than the spontaneous recovery after suxamethonium chloride (succinylcholine).

The time to reverse neuromuscular blockade with sugammadex 2 mg/kg administered at the reappearance of T2 following rocuronium 0.6 mg/kg was slower in elderly than in younger adult patients; however, reversal was reached in <4 minutes in the majority (75.5%) of elderly patients. In infants, children, adolescents and adults receiving sugammadex 2 mg/kg following rocuronium 0.6 mg/kg, the mean time to neuromuscular blockade reversal was <1.9 minutes. The efficacy of sugammadex 2 mg/kg did not differ between patients with normal renal function and those with severe renal impairment. Underlying cardiac or pulmonary disease had no effect on the efficacy of sugammadex.

**Tolerability**

Sugammadex was generally well tolerated in clinical trials in surgical patients (including elderly or paediatric patients, or patients with renal impairment or cardiac or pulmonary disease) or healthy volunteers. The majority of adverse events considered to be related to sugammadex were mild to moderate in severity. The most commonly reported adverse events in any study group were procedural pain, nausea and vomiting. In pooled analyses, the tolerability profile of sugammadex was generally similar to that of placebo or neostigmine plus glycopyrrolate; serious adverse events were infrequent. Uncommon adverse events include anaesthetic complications and dysgeusia in awake healthy volunteers, which were more frequent with higher than recommended doses of sugammadex (≥16 mg/kg), and residual or recurrent neuromuscular blockade which was more frequent with lower than recommended doses of sugammadex (<2 mg/kg).

**1. Introduction**

Surgical patients requiring general anaesthesia often receive a neuromuscular blocking agent, in addition to an anaesthetic and an analgesic agent, as part of a ‘balanced anaesthesia’ regimen[1] modified from the ‘Liverpool Technique’. [2] The neuromuscular blockade induces a temporary paralysis that enables endotracheal intubation and artificial ventilation, and allows easier surgical access to body cavities.[3,4] Typically employed neuromuscular blocking agents include the intermediate-acting,
neuromuscular blockade induced by a nondepolarizing agent may require the use of a reversal agent, while suxamethonium chloride, because of its mechanism of action, cannot be reversed. Commonly used reversal agents are anticholinesterases (e.g. neostigmine and edrophonium), which are typically given in combination with antimuscarinic agents (e.g. glycopyrrolate and atropine).

Although suxamethonium chloride is widely used when a short period of neuromuscular blockade is desired (duration of action $\approx 9$ minutes), adverse events (e.g. malignant hyperpyrexia, increased intraocular pressure and life-threatening hyperkalaemia) and contraindications (e.g. patients with major burns, crush injury or neuromuscular disease) limit its use. Nondepolarizing neuromuscular blocking agents (e.g. rocuronium) are not associated with these adverse events or contraindications, but because of longer durations of action ($\geq 20$ minutes), may require the use of a reversal agent to minimize the postoperative effects (e.g. hypoventilation, airway obstruction and hypoxia) of residual neuromuscular blockade.

However, the commonly used anticholinesterase reversal agents, because of their action at nicotinic and muscarinic receptors, are associated with adverse events such as hypotension and bradycardia. The addition of antimuscarinic agents to counteract some of these adverse events is, in turn, associated with other adverse events (e.g. blurred vision, dry mouth, tachycardia). In addition, anticholinesterase agents cannot reverse deep (profound, i.e. administration at 1–2 post-tetanic counts [PTC] after the last dose of neuromuscular blocking agent) levels of neuromuscular blockade because they reach a ‘ceiling effect’, a result of the limited levels of acetylcholine at the neuromuscular junction. Therefore, there is a clinical need for a reversal agent with a better tolerability profile and the capacity to reverse deep neuromuscular blockade.

Recent research has focused on cyclodextrins that can ‘remove’ steroidal neuromuscular blocking agents (e.g. rocuronium and vecuronium) from the neuromuscular junction, rather than mitigating the effects by increasing the amount of acetylcholine competing with the neuromuscular blocking agent at the nicotinic receptor. Cyclodextrins have been safely employed in the food, cosmetic and pharmaceutical industries since the 1970s. $\gamma$-Cyclodextrins have a lipophilic interior and a hydrophilic exterior surface; consequently, these molecules are water soluble and have been used as hydrophilic carriers for hydrophobic drugs and to enhance the permeability of hydrophilic drugs.

Sugammadex (Bridion), a modified $\gamma$-cyclodextrin, is the first of a new class of neuromuscular reversal agents, a selective relaxant binding agent. This review focuses on the pharmacological properties, therapeutic efficacy and tolerability of sugammadex in anaesthetic practice.

2. Pharmacodynamic Properties

Sugammadex (previously Org 25969) is a modified $\gamma$-cyclodextrin and has a circular structure with eight adjoining glucose molecules (figure 1). The key pharmacodynamic properties of sugammadex are presented in table I.

![Fig. 1. Sugammadex.](image-url)
Table 1. Summary of the pharmacodynamic properties of sugammadex (SUG)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro binding kinetics</strong></td>
<td></td>
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<tr>
<td>Selective, strong ($K_a 1.05 \times 10^7 \text{mol/L}$) \cite{16,21} but reversible ($K_d \approx 0.1 \mu\text{mol/L}$) binding to ROC; binds in a 1:1 ratio \cite{14}</td>
<td></td>
</tr>
<tr>
<td>Higher affinity for ROC than for other steroidal compounds, such as aldosterone, cortisol or hydrocortisone (affinities &gt;120 times lower), or nonsteroidal drugs that can form complexes with SUG, including atropine, verapamil, phenolamine, naloxone and ketamine (affinities at least 400–700 times lower) \cite{21}</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Inactivates ROC by encapsulating (chelating) the free molecule to form a stable complex \cite{16}</td>
</tr>
<tr>
<td>The resulting reduction in free ROC plasma concentration creates a gradient between the tissue compartment (including the neuromuscular junction) and plasma; free ROC is believed to move from tissue to plasma, with a reduction in nicotinic receptor occupancy at the neuromuscular junction \cite{22,23}</td>
<td></td>
</tr>
<tr>
<td><strong>Reversal of neuromuscular blockade</strong></td>
<td></td>
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<tr>
<td>Reversal activity against ROC-induced neuromuscular blockade of the same magnitude as that with neostigmine in vitro ($EC_{50} 1.2$ vs $0.9 \mu\text{mol/L}$ and $95%$ vs $74%$ maximum reversal \cite{16,18} [mouse hemidiaphragm model]) \cite{15,16} and in vivo ($ED_{50} 0.03$ vs $0.04 \mu\text{mol/kg}$ and $93%$ vs $85%$ maximum reversal \cite{15})</td>
<td></td>
</tr>
<tr>
<td>SUG reverses steroidal neuromuscular blocking agents (such as ROC) but not nonsteroidal agents (such as mivacurium or atracurium) in in vitro \cite{21} or primate \cite{25} studies</td>
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<td>When administered at a post-tetanic count of 1–2 \cite{26} or the reappearance of $T_2$ \cite{27,29} in surgical patients, SUG $0.5$–$8.0 \mu\text{g/kg}$ dose-dependently reverses the neuromuscular blockade induced by ROC $0.6$–$8.0 \mu\text{g/kg}$ or vecuronium $0.1$–$2.0 \mu\text{g/kg}$ \cite{29}</td>
<td></td>
</tr>
<tr>
<td>SUG was effective in a dose-dependent manner (range $0.16$–$16.0 \mu\text{g/kg}$) in immediate reversal of ROC $0.6$–$1.2 \mu\text{g/kg}$ in surgical patients \cite{23,30,31} or healthy volunteers \cite{32} when given $3$–$15 \mu\text{g/kg}$ or $1$–$15 \mu\text{g/kg}$ min after ROC</td>
<td></td>
</tr>
<tr>
<td>SUG reversed neuromuscular blockade during propofol-induced anaesthesia, regardless of whether anaesthesia was maintained with propofol or sevoflurane \cite{33,34}</td>
<td></td>
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<tr>
<td>At lower than recommended doses of SUG ($&lt;2 \mu\text{g/kg}$; section 6), residual neuromuscular blockade occurred in some patients in phase II dose-finding trials \cite{26,29}</td>
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<tr>
<td><strong>Cardiovascular effects</strong></td>
<td>SUG alone or with ROC or vecuronium is not associated with QTc interval prolongation in two ‘thorough QT/QTc studies’ in 146 awake healthy volunteers \cite{35} the largest mean difference to placebo in QTcl was $1.8$% vs $2.1$% msec with SUG $4 \mu\text{g/kg}$ (a recommended dose) and $2.8$% or $2.9$% msec with SUG $32 \mu\text{g/kg}$ (higher than recommended dose)</td>
</tr>
<tr>
<td>No clinically important effects of SUG on blood pressure, pulse rate, respiratory rate, body temperature, bodyweight, haematology, biochemistry or urinalysis analytes were observed in healthy volunteers who did not receive a neuromuscular blocking agent or anaesthesia \cite{38}</td>
<td></td>
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<tr>
<td>or in surgical patients (section 5.1)</td>
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</tbody>
</table>

Sugammadex was specifically designed to encapsulate the aminosteroid nondepolarizing neuromuscular blocking agent rocuronium,\cite{15} which is commonly used during anaesthesia in many countries.\cite{11} The eight side chains of sugammadex elongate the central cavity to ensure complete encapsulation of rocuronium, while negatively charged carbonyl groups at the end of each chain enhance electrostatic binding to the positively charged nitrogen atom of rocuronium.\cite{16} The structural similarity between rocuronium and vecuronium means that sugammadex also encapsulates vecuronium.\cite{21}

2.1 Mechanism of Action

The mechanism of action of sugammadex is unique among currently available neuromuscular reversal agents.\cite{7} Sugammadex selectively and reversibly binds to free rocuronium or vecuronium in plasma (table I). This sequestration reduces the amount of rocuronium or vecuronium available to bind at active sites, including nicotinic receptors at the neuromuscular junction, which results in reversal of the neuromuscular blockade induced by these drugs (table I). The resulting sugammadex-rocuronium complex is
inactive\cite{32} and is eliminated from the body according to the pharmacokinetic properties of sugammadex, not those of rocuronium (section 3).

2.2 Reversal of Neuromuscular Blockade

In in vitro and animal studies, sugammadex demonstrated reversal activity against rocuronium-induced neuromuscular blockade as effective as that achieved with neostigmine (table I). In partially\cite{29} or fully\cite{23,26,28-30,31} randomized, assessor-blind (some placebo-controlled\cite{23,28-31}), multicentre, phase II trials,\cite{23,26-31} sugammadex was dose-dependently effective in reversing rocuronium- or vecuronium-induced neuromuscular blockade (table I). These trials enrolled patients aged ≥18 years who were American Society of Anesthesiologists (ASA) physical status class I\textendash{}II\cite{23,28,29,31} or I\textendash{}III\cite{26,27,30} (the ASA classification is presented in table II). Discussion of efficacy data in this section will focus on pooled analyses\cite{38} of phase II and III trials at the recommended doses of sugammadex (2 mg/kg if spontaneous recovery at least to the reappearance of T2, 4 mg/kg if recovery has reached at least 1\textendash{}2 PTC or 15 minutes after rocuronium, and was 2.8 minutes with sugammadex 2 mg/kg (n = 21) and 74.2 minutes with placebo (n = 19) for reversal of vecuronium.\cite{38} When administered at 1\textendash{}2 PTC or 15 minutes after rocuronium, the time to reach TOF 0.9 was 1.8 minutes with sugammadex 4 mg/kg (n = 31) and 35.6 minutes with placebo (n = 3); the time to reach TOF 0.9 with administration at 1\textendash{}2 PTC following vecuronium was 3.2 minutes with sugammadex 4 mg/kg (n = 18) and 73.0 minutes with placebo (n = 12). The time to reach TOF 0.9 when administered 3 or 5 minutes after rocuronium 1.2 mg/kg was 1.6 minutes with sugammadex 16 mg/kg (n = 18) and 122.5 minutes with placebo (n = 8).\cite{38}

Using the calculation of tolerance intervals, it is expected (with 97.5\% confidence) that after a dose of sugammadex 2 mg/kg administered at the reappearance of T2, 90\% of individuals will reach TOF 0.9 or better within 3.0 minutes when reversing rocuronium, and within 5.9 minutes when reversing vecuronium.\cite{38} Similarly, when sugammadex 4 mg/kg is administered at 1\textendash{}2 PTC after rocuronium-induced neuromuscular blockade, or at 15 minutes after administration of rocuronium 0.6 mg/kg, 90\% of individuals are expected to reach TOF 0.9 or better within 3.9 minutes. The optimal dosages identified in these trials were employed in phase III trials (section 4) and were subsequently approved by the European Medicines Agency (EMEA) [section 6].

2.3 Other Effects

Two ‘thorough QT/corrected QT (QTc) studies’ in awake, healthy volunteers showed no QTc interval prolongation with the use of sugammadex (table I), conducted in accordance with E14 guidelines.\cite{41} In clinical trials in which sugammadex was given in combination with propofol or sevoflurane (both of which have the potential to prolong QTc interval) to surgical patients, very few patients had

<table>
<thead>
<tr>
<th>Table II. American Society of Anesthesiologists physical status classification system\cite{40}</th>
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<tr>
<td>Class</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
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<tr>
<td>III</td>
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<td>IV</td>
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<td>V</td>
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<td>VI</td>
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</tbody>
</table>

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evidence of QTc interval prolongation (QTc >500 msec or QTc increases >60 msec). In addition, there was no clinically significant prolongation of the QT interval in a subgroup of surgical patients with severe heart disease who received sugammadex (section 5.2).

No clinically relevant effects of sugammadex on liver or kidney function were reported in pooled data of phase II and III trials.

Preclinical testing of safety, repeated-dose toxicology, genotoxicity potential, toxicity to reproduction, local tolerance or food compatibility revealed no special hazard of sugammadex to humans.

After repeated administration of sugammadex with drug exposure equivalent to 48–480 times that of a clinical dose of 4 mg/kg, some adverse retention effects were observed in the teeth of juvenile (but not adult) rats.

Sugammadex, unlike neostigmine, did not impair upper airway dilator muscle activity and breathing when administered to anaesthetized rats.

### 2.4 Pharmacodynamic Drug Interactions

The potential drug interactions of sugammadex discussed in this section are based on binding affinity between sugammadex and other medicinal products, simulation, modelling and in vitro data, not clinical experience.

Administration of toremifene, fusidic acid or flucloxacillin may affect the efficacy of sugammadex. Toremifene may displace rocuronium or vecuronium bound to sugammadex, as it has a relatively high affinity constant and achieves high plasma concentrations; patients receiving toremifene on the same day as sugammadex may experience a delay in the reversal of neuromuscular blockade. Postoperative intravenous administration of fusidic acid or high-dose (≥500 mg) flucloxacillin may displace rocuronium or vecuronium bound to sugammadex; therefore, the use of these drugs within 6 hours postoperatively should be avoided. Close monitoring for signs of re-occurrence of neuromuscular blockade, especially within 15 minutes of administration of fusidic acid or flucloxacillin, is recommended if the use of these drugs cannot be avoided.

Administration of sugammadex on the same day as a dose of an oral contraceptive steroid (combined or progestogen only) has the same effect as a missed dose of the contraceptive. Sugammadex 4 mg/kg is predicted to reduce progestogen exposure (as assessed by area under the concentration-time curve [AUC]) by 34% and lead to reduced efficacy of progestogen. Patients receiving sugammadex on the same day as taking a dose of oral or non-oral hormonal contraceptives should be referred to the appropriate package insert for instructions relevant to a missed dose.

Although sugammadex does not interfere with laboratory tests in general, some interference was observed with the serum progesterone assay and some coagulation parameters (sugammadex was added to these samples at the same maximum plasma concentration range as that following a dose of 16 mg/kg); however, the clinical relevance of these results has not been determined.

### 3. Pharmacokinetic Properties

The pharmacokinetic properties of sugammadex have been evaluated in phase I, phase II and phase III trials; other data discussed in this section were obtained from the EMEA summary of product characteristics (SPC). Discussion focuses on sugammadex and the sugammadex-rocuronium complex; the pharmacokinetic properties of the sugammadex-vecuronium complex and the effects of sugammadex on the pharmacokinetic properties of vecuronium have not been evaluated.

Intravenous sugammadex demonstrates linear pharmacokinetic properties over the dose range of 1–16 mg/kg when administered as an intravenous bolus. The pharmacokinetics of single-dose sugammadex 2 or 4 mg/kg are presented in table III.

The apparent volume of distribution at the terminal phase of sugammadex is 18 L (0.26 L/kg) and at steady state (Vdss) is 11–14 L (0.16–0.20 L/kg) both after a single dose. In in vitro studies of human plasma and whole blood, sugammadex (in free form or as a complex with rocuronium) does not bind to plasma proteins or erythrocytes.

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It is assumed that sugammadex does not undergo metabolism as metabolites of sugammadex have not been detected in preclinical or clinical studies.\[35\]

Only renal excretion of the unchanged drug has been observed as the route of elimination for sugammadex.\[35\] In healthy adult volunteers, the terminal elimination half-life ($t_{1/2}$) of sugammadex is 1.8 hours.\[35\] The majority (>90%) of a dose of sugammadex is excreted within 24 hours of administration.\[35\] Sugammadex is primarily (96%) excreted in the urine, predominantly (>95%) as the unchanged drug; excretion in the faeces or expired air was minimal (0.02%).\[35\] The plasma clearance (CL) of sugammadex is 84–138 mL/min in adults with normal renal function (table III).

### Table III. Key pharmacokinetic parameters of single-dose intravenous sugammadex (SUG) and rocuronium (ROC) in healthy volunteers or surgical patients with or without severe renal impairment. All pharmacokinetic data are geometric mean values

<table>
<thead>
<tr>
<th>Regimen (mg/kg) or group</th>
<th>No. in group</th>
<th>AUC$_\infty$ (µg • min/mL)</th>
<th>Vd (L)</th>
<th>CL (mL/min)</th>
<th>MRT (h)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
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<tbody>
<tr>
<td><strong>SUG</strong></td>
<td></td>
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<tr>
<td>In healthy volunteers[32]</td>
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<td></td>
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<tr>
<td>SUG 2[b]</td>
<td>6</td>
<td>1 100</td>
<td>20.9</td>
<td>138.0</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>SUG 4[b]</td>
<td>5</td>
<td>2 627</td>
<td>17.7</td>
<td>118.0</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>ROC 0.6 + SUG 2</td>
<td>2</td>
<td>1 573</td>
<td>15.1</td>
<td>94.5</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>ROC 0.6 + SUG 4</td>
<td>2</td>
<td>3 494</td>
<td>14.6</td>
<td>84.8</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>In surgical patients[44]c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>1 728</td>
<td>13.8</td>
<td>95.2</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Renally impaired</td>
<td>13</td>
<td>27 463*</td>
<td>16.0*</td>
<td>5.5*</td>
<td>48.2*</td>
<td>35.7*</td>
</tr>
<tr>
<td><strong>ROC</strong></td>
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<tr>
<td>In healthy volunteers[32]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ROC 0.6 + SUG 2</td>
<td>2</td>
<td>302</td>
<td>15.1</td>
<td>155.0</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>ROC 0.6 + SUG 4</td>
<td>2</td>
<td>364</td>
<td>12.5</td>
<td>121.0</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>ROC 0.6 + PL</td>
<td>10</td>
<td>139</td>
<td>49.3</td>
<td>327.0</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>In surgical patients[44]c</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Control</td>
<td>13</td>
<td>296</td>
<td>19.1</td>
<td>167.0</td>
<td>1.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Renally impaired</td>
<td>13</td>
<td>1 084*</td>
<td>22.1*</td>
<td>41.8*</td>
<td>8.8*</td>
<td>7.5*</td>
</tr>
</tbody>
</table>

\[a\] A randomized, crossover, phase I study in healthy volunteers given SUG or PL, with or without general anaesthesia (propofol and remifentanil) and ROC; in those who received ROC, SUG or PL was given 3 min after ROC administration. Data from SUG 0.1–1 mg/kg and 8 mg/kg dose groups are not presented.

\[b\] Individuals who did not receive anaesthesia.

\[c\] A nonrandomized phase III trial in surgical patients with normal renal function (CL$_{CR}$ ≥80 mL/min; American Society of Anesthesiologists [ASA] classes I–II) or severe renal impairment (CL$_{CR}$ <30 mL/min; ASA classes II–III) who received propofol and opiates for anaesthesia and ROC with SUG administered at the reappearance of T$_2$.

AUC$_\infty$ = area under the plasma concentration-time curve from time zero to infinity; CL = plasma clearance; CL$_{CR}$ = creatinine clearance; MRT = mean residence time; PL = placebo; $t_{1/2}$ = terminal elimination half-life; T$_2$ = the second response in the train-of-four stimulation; Vd = apparent volume of distribution; * p ≤ 0.05 vs control group.

3.1 Effects on the Pharmacokinetic Properties of Rocuronium

The pharmacokinetic properties of rocuronium have been reviewed previously,\[45,46\] and a detailed account is beyond the scope of this review. Rocuronium, like sugammadex, is primarily excreted unchanged, indicating that it undergoes minimal metabolism;\[45,47\] no metabolites have been detected in plasma.\[12\] Rocuronium is excreted in urine and bile, with ~40% of a dose excreted within 24 hours in urine.\[12\] At 9 days after administration of radiolabelled rocuronium, 47% of a dose is excreted in urine and 43% in faeces; 50% of the drug is excreted as the parent compound.\[12\] As discussed previously (table I), quantitative assessment of the plasma concentrations of rocuronium, when
administered with sugammadex, cannot distinguish between free rocuronium and rocuronium in complex with sugammadex. The volume of distribution of rocuronium is decreased with the addition of sugammadex compared with the addition of placebo (table III). Administration of sugammadex following that of rocuronium increases the plasma concentration (in a manner dependent on the dose of sugammadex), AUC from time zero to infinity and mean residence time of rocuronium (table III); however, these increases do not lead to an enhancement, but a decline, in the neuromuscular blockade induced by rocuronium (section 2), indicating that the increased plasma concentration of rocuronium is not due to active, free rocuronium molecules, but to inactive, sugammadex-bound molecules.

Sugammadex increases the urinary excretion of rocuronium, and the t1/2β of rocuronium is reduced by »30% with the addition of sugammadex compared with that of rocuronium with placebo (table III). Administration of rocuronium and sugammadex 2 or 4 mg/kg was associated with a 2- to 3-fold increase in urinary excretion of rocuronium in the first 24 hours compared with rocuronium plus placebo in healthy volunteers (32% or 44% vs 14% of a dose) or in surgical patients (42% or 53% vs 19%) in the first 16 hours. The effect of sugammadex on the urinary excretion of rocuronium appears to be dose dependent.

The CL of rocuronium is reduced »2 fold with the addition of sugammadex (table III). Although rocuronium is partly eliminated via the biliary route, sugammadex and the sugammadex-rocuronium complex are not; therefore, sugammadex-bound rocuronium appears to be limited to elimination in the urine.

3.2 Special Patient Populations

The elimination of sugammadex or the sugammadex-rocuronium complex was significantly delayed in patients with severe renal impairment (creatinine clearance [CLCR] <30 mL/min) compared with patients with normal renal function (CLCR ≥80 mL/min) as reflected by the significantly reduced CL and significantly greater mean residence time and t1/2β (table III). However, the efficacy of sugammadex was not affected (section 4.2) and neuromuscular blockade did not reoccur (section 5.2) in these patients. The use of sugammadex in patients with severe renal impairment, including those needing dialysis, is associated with inconsistent decreases in plasma sugammadex concentration; therefore, the use of sugammadex in patients with severe renal impairment is not recommended (section 6).

As the hepatic route is not involved in the metabolism or excretion of sugammadex, the use of sugammadex has not been evaluated in patients with hepatic impairment; however, caution is recommended for the use of sugammadex in patients with severe hepatic impairment.

The pharmacokinetics of sugammadex in the intensive care setting have not been evaluated. Based on pharmacokinetic modelling, in an elderly (aged 75 years) patient with normal renal function (CL_CR 100 mL/min), CL, Vdss and t1/2β values of sugammadex were generally similar to those in an adult (aged 40 years) patient with normal renal function (80 vs 88 mL/min, 13.5 vs 11.4 L and 2.4 vs 1.8 h, respectively). Although the pharmacokinetic parameters of sugammadex in elderly patients may be affected by renal impairment, the estimated CL and t1/2β values did not differ markedly from those in younger patients with renal impairment.

In paediatric patients, CL, Vdss and t1/2β values increase with patient age. For example, at 8 years of age, these values are 41 mL/min, 3.1 L and 0.9 hours, respectively, compared with 71 mL/min, 9.1 L and 1.7 h at age 15 years. In paediatric patients, variations in plasma concentrations are similar to those seen in adult patients. Sugammadex is currently not recommended for use in patients aged <2 years (section 6) because of a lack of data in this patient population.

No clinical data are available for the use of sugammadex in pregnant women and caution is advised. It is not known if sugammadex is excreted in human breast milk, but because cycloextrinsics generally have low absorption, a single dose of sugammadex in breast feeding women is not expected to adversely affect the child.
No clinically relevant differences were observed on the basis of patient sex, race or bodyweight.[35]

4. Therapeutic Efficacy

The clinical efficacy of sugammadex has been investigated in four randomized, assessor-blind, multicentre, phase III trials[50-55] (section 4.1), an open-label, supporting trial (with data from a single centre[56] or multiple centres[57]) [section 4.1], and five trials[42,48,49,58,59] and a pooled analysis[60] in special patient populations (section 4.2). Some data are fully published[48,49,51-53,56] and the remainder are available as abstracts and posters.[42,50,54,55,57-60] Pooled analyses of efficacy data were obtained from the US FDA briefing document[38] (section 4.3).

All trials enrolled adult patients, aged 18–65 years[49,53] or >18 years,[42,48,50-52,54,55,58,59] although two trials also included elderly (aged >65 years)[58] or paediatric (aged 28 days to 18 years)[49] patients. Enrolled patients were ASA class I–II,[49,53] I–III,[48,50-52,54-58] II–III[59] or II–IV[42] (table II), undergoing surgery in the supine position and requiring general anaesthesia, including neuromuscular blockade. Three trials enrolled patients with severe renal impairment (CLCR <30 mL/min),[48] cardiac disease (e.g. arrhythmia, chronic heart failure or ischaemic heart disease)[43] or a history/diagnosis of pulmonary disease (e.g. asthma, chronic obstructive pulmonary disease or bronchitis).[59]

Where reported,[48,51,52] the trials excluded patients with neuromuscular disease or patients expected to have a difficult intubation due to anatomical reasons.

In the comparative phase III trials,[50-57] patients received rocuronium or vecuronium for neuromuscular blockade, although two rocuronium trials also included elderly (aged >65 years)[58] or paediatric (aged 28 days to 18 years)[49] patients. Enrolled patients were ASA class I–II,[49,53] I–III,[48,50-52,54-58] II–III[59] or II–IV[42] (table II), undergoing surgery in the supine position and requiring general anaesthesia, including neuromuscular blockade. Three trials enrolled patients with severe renal impairment (CLCR <30 mL/min),[48] cardiac disease (e.g. arrhythmia, chronic heart failure or ischaemic heart disease)[43] or a history/diagnosis of pulmonary disease (e.g. asthma, chronic obstructive pulmonary disease or bronchitis).[59]

Where reported,[48,51,52] the trials excluded patients with neuromuscular disease or patients expected to have a difficult intubation due to anatomical reasons.

In the comparative phase III trials,[50-57] patients received rocuronium or vecuronium for neuromuscular blockade, although two rocuronium trials included a cisatracurium[51] or suxamethonium chloride[53] arm; to reverse neuromuscular blockade, patients received sugammadex or neostigmine plus glycopyrrolate (or edrophonium plus atropine in a third arm of one trial[56]). In addition, another trial[53] assessed spontaneous recovery in the suxamethonium chloride arm. In trials with special patient populations,[42,48,49,58,59] all patients received rocuronium, and sugammadex or sugammadex or placebo in two[42,49] of these trials. Full dosage and administration details of the main phase III trials are shown in table IV, while those of the supporting trial and studies in special patient populations are discussed in section 4.1 and section 4.2, respectively. Anaesthesia was induced with propofol (and maintained with propofol or sevoflurane) and an analgesic agent (including fentanyl, remifentanil, sufentanil or unspecified opioid) according to each patient’s individual needs.[42,48,55,58,59] Acceleromyography (TOF-Watch® SX) was employed to monitor neuromuscular function in all trials; acceleromyography is a recommended option for the assessment of neuromuscular function in clinical trials.[61]

The primary efficacy endpoint was the time from administration of the reversal agent to neuromuscular blockade reversal (as assessed by time to reach TOF 0.9);[48-52,54-58] TOF 0.9 is the currently recommended threshold of adequate recovery.[61] In the trial with the suxamethonium chloride arm,[53] where TOF assessment is not appropriate, the primary efficacy endpoint was the time from administration of the neuromuscular blocking agent until reversal or spontaneous recovery (as assessed by the time of the first twitch of the TOF stimulation [T1] to reach 10% [i.e. the recovery of the amplitude of T1 to reach 10% of that at baseline]). Safety was the primary endpoint for the cardiac trial[42] and pulmonary trial[59] disease trials, although both trials also assessed the time to reach TOF 0.9. Secondary endpoints included time to reach a TOF ratio of 0.8 (TOF 0.8) and 0.7 (TOF 0.7).[48-52,54,56,57] For the time to reach TOF 0.9, TOF 0.8 and TOF 0.7, geometric mean[42,50-52,54,55,58,59] or arithmetic mean[48,49] values were reported for the intent-to-treat population; statistical significance of the geometric mean was calculated using analysis of variance on log transformed recovery times. Geometric mean values were considered more appropriate in most trials, as the distribution of the data was skewed.[50,51,54] For the time to reach T1 of 10% or 90%,[53] mean and median values were reported and statistical significance was calculated using
Table IV. Efficacy of sugammadex (SUG) in reversing neuromuscular blockade (NMB) induced by rocuronium (ROC) or vecuronium (VEC) in adult (aged >18 years) surgical patients (pts) requiring general anaesthesia. Pts in four randomized, assessor-blind, multicentre, phase III trials were given neuromuscular blocking agents (NMBAs) as a single intravenous bolus dose; maintenance dosages of ROC 0.1–0.2 mg/kg; VEC 0.02–0.03 mg/kg or cisatracurium (CIS) 0.03 mg/kg were permitted as required. In all trials, anaesthesia was induced with propofol (and maintained with propofol or sevoflurane) and an analgesic agent (including fentanyl, remifentanil, sufentanil or unspecified opioid) according to each pt’s individual needs; neuromuscular function was monitored by acceleromyography (TOF-Watch® SX).

<table>
<thead>
<tr>
<th>Study (name)</th>
<th>NMB protocol (mg/kg)</th>
<th>No. of pts</th>
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<tr>
<td></td>
<td>NMBA reversal agent</td>
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<td>NMBA reversal agent</td>
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<td></td>
<td>Time to reach NMB reversal (geometric mean; min) [range]</td>
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<td></td>
<td>as assessed by TOF ratio&lt;br&gt;(to 0.9)</td>
<td>as assessed by T&lt;sub&gt;1&lt;/sub&gt;&lt;br&gt;(to 10%)</td>
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<td>to 0.8</td>
<td>to 0.7</td>
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### Reversal of ROC

**SUG or NEO + GLY administered at the reappearance of T<sub>2</sub>**

- **Blobner et al.**<sup>[50]</sup>: ROC 0.6 SUG 2.0
  - 48 pts
  - 1.5<sup>a</sup> [0.9–5.4] 1.3<sup>a</sup> [0.9–3.4] 1.1<sup>a</sup> [0.7–2.7]

- **AURORA**
  - ROC 0.6 NEO 0.05 + GLY 0.01
  - 48 pts
  - 18.5<sup>c</sup> [3.7–106.9] 10.8 [2.7–67.9] 7.2 [2.4–41.1]

- **Flockton et al.**<sup>[51]</sup>: ROC 0.6 NEO 0.05 + GLY 0.01
  - 32 pts
  - 1.9<sup>c</sup> [0.7–6.4] 1.6<sup>c</sup> [0.7–3.4] 1.4<sup>c</sup> [0.7–2.9]

- **CRYSTAL**
  - CIS 0.15 NEO 0.05 + GLY 0.01
  - 34 pts

**SUG or NEO + GLY administered at a post-tetanic count of 1–2**

- **Jones et al.**<sup>[52]</sup>: ROC 0.6 SUG 4.0
  - 37 pts
  - 2.9<sup>d</sup> [1.2–16.1] 2.4 [1.1–10.1] 2.0 [1.0–7.8]

- **SIGNAL**
  - ROC 0.6 NEO 0.07 + GLY 0.014
  - 37 pts
  - 50.4<sup>c</sup> [13.3–145.7] 40.6 [11.3–143.7] 32.6 [9.3–123.2]

**SUG administered 3 min after the start of ROC administration**

- **Lee et al.**<sup>[53]</sup>: ROC 1.2 SUG 16.0
  - 55 pts
  - 2.2 1.5 1.3
  - 4.4<sup>d</sup> [3.5–7.7] 6.2 [4.2–13.6]

- **SPECTRUM**
  - SUX 1.0 None<sup>e</sup>
  - 55 pts
  - 7.1<sup>d</sup> [3.8–10.5] 10.9 [5.0–16.2]

### Reversal of VEC

**SUG or NEO + GLY administered at the reappearance of T<sub>2</sub>**

- **Alvarez-Gómez et al.**<sup>[54]</sup>: VEC 0.1 SUG 2.0
  - 48 pts
  - 2.8<sup>d</sup> [1.2–64.2] 2.0<sup>d</sup> [1.0–4.3] 1.6<sup>d</sup> [0.7–3.4]

- **AURORA**
  - VEC 0.1 NEO 0.05 + GLY 0.01
  - 45 pts
  - 16.8<sup>d</sup> [2.9–76.2] 10.2 [2.2–59.1] 6.1 [1.9–54.3]

**SUG or NEO + GLY administered at a post-tetanic count of 1–2**

- **Lemmens et al.**<sup>[55]</sup>: VEC 0.1 SUC 4.0
  - 47 pts
  - 4.5<sup>d</sup> [1.4–68.4]

- **SIGNAL**
  - VEC 0.1 NEO 0.07 + GLY 0.014
  - 36 pts
  - 66.2<sup>d</sup> [46.0–312.7]

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- **a** Reported values refer to the primary efficacy, intent-to-treat population.
- **b** Measured from administration of the reversal agent to neuromuscular blockade reversal. TOF ratio of 0.9 represents the time when the amplitude of the fourth twitch divided by that of the first twitch of the TOF stimulation is 0.9.
- **c** Measured from administration of the NMBA until reversal of the blockade. T<sub>1</sub> to 10% represents the time when the amplitude of T<sub>1</sub> is 10% of that at baseline.
- **d** Primary efficacy endpoint.
- **e** Neuromuscular activity was allowed to recover spontaneously.

**GLY** = glycopyrrolate; **NEO** = neostigmine; **SUX** = suxamethonium chloride (succinylcholine); **T<sub>1</sub>** = the first twitch in the TOF stimulation; **T<sub>2</sub>** = the second twitch in the TOF stimulation; **TOF** = train-of-four; *p < 0.0001 SUG vs comparator.
analysis of variance. Equivalence of the efficacy of sugammadex in patients with renal impairment versus those with normal renal function was established if the 95% CI of the between-group difference was <60 seconds.[48]

4.1 In Adult Patients

Routine reversal of moderate (shallow, i.e. administration at reappearance of T2) or deep rocuronium-induced neuromuscular blockade was significantly more rapid with sugammadex than with neostigmine plus glycopyrrolate. The reversal of rocuronium 0.6 mg/kg-induced neuromuscular blockade with sugammadex 2 mg/kg given at the reappearance of T2 (moderate blockade) occurred within a mean of 2 minutes after administration and was 12 times faster than that with neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg (table IV).[50] Similarly, the reversal of rocuronium-induced neuromuscular blockade with sugammadex 4 mg/kg given at the reappearance of 1–2 PTC (deep blockade)[52] was 17 times more rapid that that with neostigmine 70 µg/kg plus glycopyrrolate 14 µg/kg (table IV).[52]

The reversal of moderate rocuronium-induced neuromuscular blockade by sugammadex was significantly faster than the reversal of moderate cisatracurium-induced neuromuscular blockade by neostigmine plus glycopyrrolate. A standard dose of rocuronium 0.6 mg/kg was reversed by sugammadex 2 mg/kg in approximately one-fifth of the time required for neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg to reverse cisatracurium 0.15 mg/kg, given at the reappearance of T2 (table IV).[51]

As assessed using TOF 0.8 and TOF 0.7 (secondary endpoints), the reversal of moderate[50] or deep[52] rocuronium-induced neuromuscular blockade with sugammadex was faster than that with neostigmine plus glycopyrrolate, and reversal of moderate rocuronium-induced neuromuscular blockade with sugammadex was faster than moderate cisatracurium-induced neuromuscular blockade with neostigmine plus glycopyrrolate[51] (table IV).

The time to reverse a high dose of rocuronium 1.2 mg/kg with sugammadex 16 mg/kg (given 3 minutes after rocuronium) was significantly shorter (by ~40%) than that of spontaneous recovery of suxamethonium chloride 1 mg/kg, as assessed by the recovery of T1 to 10% (primary endpoint) and by T1 to 90% (secondary endpoint) [table IV].[53] Rocuronium 1.2 mg/kg was used because this dose induces intubating conditions similar to those induced with suxamethonium chloride.[38] When assessed using the time to reach TOF 0.9, the time to reverse a high dose of rocuronium 1.2 mg/kg with a high dose of sugammadex 16 mg/kg administered after 3 minutes of rocuronium was <2.5 minutes (table IV).

Results of the open-label trial[56,57] in which sugammadex was given at least 15 minutes after the last dose of rocuronium confirm the efficacy of sugammadex seen in the randomized trials. In the single-centre report (n = 60),[56] the time to reach TOF 0.9 after rocuronium 0.6 mg/kg was significantly shorter with sugammadex 4 mg/kg (1.8 minutes) than with neostigmine 70 µg/kg plus glycopyrrolate 14 µg/kg (17.4 minutes) or edrophonium 1 mg/kg plus atropine 10 µg/kg (5.5 minutes) [all p < 0.05]. Significant differences between sugammadex and the comparators were observed for the time to reach TOF 0.8 and TOF 0.7 (all p < 0.05).[56] In a noncomparative analysis of all study centres (n = 197) [available as an abstract and poster],[57] the recovery of neuromuscular function following administration of rocuronium 0.6 mg/kg with sugammadex 4 mg/kg was rapid, as assessed by geometric mean time to reach TOF 0.9 (1.9 minutes), TOF 0.8 (1.5 minutes) and TOF 0.7 (1.3 minutes).

Sugammadex was significantly faster than neostigmine plus glycopyrrolate in reversing moderate or deep vecuronium-induced neuromuscular blockade in phase III trials. The time to reverse vecuronium 0.1 mg/kg with sugammadex 2 mg/kg given at the reappearance of T2 (moderate blockade) was <3 minutes, and was one-sixth of that seen with neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg (primary endpoint; table IV).[54] Time to reach TOF 0.8 and TOF 0.7 (secondary endpoints) were significantly faster with sugammadex than with...
neostigmine plus glycopyrrolate (table IV). The time to reverse deep vecuronium-induced neuromuscular blockade with sugammadex 4 mg/kg (administered at the reappearance of 1–2 PTC) was ≈15 times shorter than that with neostigmine 70 μg/kg plus glycopyrrolate 14 μg/kg (table IV). [55]

4.2 In Special Patient Populations

In all trials with special patient populations,[42,48,49,58,59] all patients received rocuronium 0.6 mg/kg as a single intravenous bolus, with maintenance of 0.1–0.2 mg/kg [42,58,59] if required. The trial enrolling paediatric patients was a dose-finding phase III trial; [49] although other sugammadex doses (0.5, 1.0 and 4.0 mg/kg) were also evaluated in this trial, they are not discussed further as 2 mg/kg is the only recommended dose for use in paediatric patients (see section 6). Two trials [42,49] included a placebo arm. In all trials, sugammadex 2 or 4 mg/kg was administered as a single intravenous bolus at the reappearance of T2. The primary endpoint was either the time to reach TOF 0.9 or safety (discussed in section 5). Secondary endpoints included time to reach TOF 0.8 and TOF 0.7 or time to reach TOF 0.9 in the safety trials. [42,59]

Sugammadex was effective in older patients, but was associated with a slower reversal of rocuronium-induced neuromuscular blockade compared with younger adult patients. The recovery of TOF 0.9 with sugammadex 2 mg/kg was reached in a geometric mean time of 2.3 minutes in younger adult patients (aged 18–64 years; n = 48) compared with 2.6 minutes in elderly patients (aged 65–74 years; n = 62) and 3.6 minutes in those aged ≥75 years (n = 40) [no p-values reported]. [58] The median recovery time in younger adults (aged 18–64 years) was faster than in elderly (aged ≥65 years) patients (2.2 vs 2.9 minutes; p = 0.022). Nevertheless, the majority of patients reached TOF 0.9 in <4 minutes (85.4% of younger adult and 75.5% of elderly patients). The time to reach TOF 0.9 was generally similar between patients receiving only an intubating dose and those also receiving maintenance doses of rocuronium for all age groups (exploratory endpoint). [58]

Sugammadex was an effective reversal agent of rocuronium-induced neuromuscular blockade in paediatric patients. The mean time to reach TOF 0.9 with sugammadex 2 mg/kg in infants (aged 28 days to 23 months; n = 1), children (2–11 years; n = 4), adolescents (12–17 years; n = 6) and adults (18–65 years; n = 5) was 0.6 minutes in infants and 1.1–1.9 minutes in children, adolescents and adults versus 19.6–29.5 minutes with placebo (n = 2 infants, 4 children, 5 adolescents and 6 adults) [range 0.6–5.2 minutes with sugammadex vs 6.8–44.0 minutes with placebo]. [49]

The efficacy of sugammadex in reversing rocuronium-induced neuromuscular blockade did not differ significantly between patients with normal renal function and those with severe renal impairment. The mean time to reach TOF 0.9 with sugammadex 2 mg/kg was 1.6 minutes in patients with normal renal function (CLCR ≥80 mL/min; n = 14) and 2.0 minutes in those with renal failure (CLCR <30 mL/min; n = 15). [48] However, equivalence was not established for the mean absolute difference between the renal and control groups (27.3 seconds) [95% CI −10.9, 65.5].

Pre-existing cardiac or pulmonary disease did not affect the efficacy of sugammadex in reversing rocuronium-induced neuromuscular blockade. In patients with cardiac disease, [42] the geometric mean time to reach TOF 0.9 was 1.7 minutes (n = 37) with sugammadex 2 mg/kg, 1.4 minutes (n = 36) with sugammadex 4 mg/kg and 34.3 minutes (n = 36) with placebo. In patients with pulmonary disease, [59] the geometric mean time to reach TOF 0.9 was 2.1 minutes (n = 39) with sugammadex 2 mg/kg and 1.8 minutes (n = 38) with sugammadex 4 mg/kg. Obesity did not affect the efficacy of sugammadex in reversing rocuronium- or vecuronium-induced neuromuscular blockade. In a pooled analysis of 18 clinical trials, no significant difference in the time to reach TOF 0.9 was observed between non-obese (median body mass index [BMI] 24.9–25.7 kg/m²) and obese (BMI 31.7–38.6 kg/
patients receiving sugammadex 2 mg/kg at the reappearance of T2 following administration of rocuronium (geometric mean of 2.1 vs 2.1 minutes) or vecuronium (2.9 vs 2.4 minutes), sugammadex 4 mg/kg at 1–2 PTC following administration of rocuronium (2.0 vs 3.0 minutes) or vecuronium (3.9 vs 4.0 minutes) or sugammadex 16 mg/kg 3 minutes after the administration of rocuronium (1.7 vs 2.2 minutes) [all p ≥ 0.09].

4.3 Pooled Analyses

The shorter time to recovery observed with sugammadex compared with other neuromuscular blockade reversal agents (when administered at the reappearance of T2) in reversing moderate rocuronium-induced neuromuscular blockade in a pooled analysis[38] of phase II[27–29,33] (including unpublished data[38]) and phase III[42,48–51,54,58,59] trials (figure 2) was considered clinically relevant.[38]

Data from a pooled analysis[38] of phase II[29] (including unpublished data[38]) and phase III[50,54] trials in which sugammadex was administered at the reappearance of T2 also demonstrate a clinically relevant difference between sugammadex and neostigmine plus glycopyrrolate or placebo in reversing moderate vecuronium-induced neuromuscular blockade (figure 3).

5. Tolerability

The tolerability data for sugammadex in surgical patients discussed in this section were obtained from phase III trials[42,48–59] (section 4), other clinical trials[23,28–32] (section 2), including two high-dose studies (one published[62] and the other available as an abstract and poster[63]), a case report[64] and the EMEA SPC.[35] Pooled analyses of tolerability were primarily obtained from the FDA briefing document[38] and the EMEA scientific document[65] and were supplemented with an abstract and poster[66].

Pooled analyses discussed in this section were obtained from phase I–III placebo-controlled
trials of sugammadex 0.1–16 mg/kg or phase III trials comparing sugammadex 2 or 4 mg/kg with neostigmine plus glycopyrrolate. In the pooled dataset from placebo-controlled trials, 640 surgical patients or healthy volunteers received sugammadex and 140 received placebo. In the pooled dataset from the comparative trials, 179 surgical patients received sugammadex and 167 received neostigmine plus glycopyrrolate. Patients and volunteers in the pooled datasets were ASA classes I–III, apart from one ASA class IV patient in the placebo-controlled trials dataset.

5.1 General Profile

Sugammadex was generally well tolerated in phase II and phase III trials, and most adverse events considered to be related to the study drug were mild to moderate in severity. As might be expected after a surgical procedure, the most commonly reported adverse events in pooled data from the placebo-controlled (figure 4) or active comparator-controlled (figure 5) trials were procedural pain, nausea and vomiting.

In pooled analyses, the tolerability profile of sugammadex was generally similar to that of placebo (figure 4) or neostigmine plus glycopyrrolate (figure 5). Adverse events were reported in 68% of sugammadex and 72% of placebo recipients in one analysis, and 88% of sugammadex versus 89% of neostigmine plus glycopyrrolate recipients in the other analysis. Pooled results showed that few sugammadex recipients experienced a serious adverse event in placebo-controlled (5.8%)}
vs 4.3% with placebo) or active comparator-controlled (3.4% vs 3.6% with neostigmine plus glycopyrrolate) trials. In all clinical trials, no deaths were considered to be related to the study medication. Dysgeusia (metallic or bitter taste perversion) was uncommon at recommended doses of sugammadex (0.0–7.1% with sugammadex ≤16 mg/kg), but was the most frequent adverse event at higher doses (15.4% with sugammadex 32 mg/kg and 66.7% with sugammadex 96 mg/kg) in awake healthy volunteers. No dose-related adverse events or serious adverse events were reported in high-dose studies in healthy volunteers with sugammadex 16, 20, 32, 64 or 96 mg/kg or with a case of inadvertent overdose with sugammadex 40 mg/kg.

Adverse events with an incidence of >2% in the sugammadex arm and occurring at least twice as frequently as with placebo included anaesthetic complication (8.0% vs 1.4%; figure 4) and cough (2.8% vs 1.4%); ~40% and ~46% of these events, respectively, were considered to be related to the use of sugammadex. Anaesthetic complications included signs of light anaesthesia (e.g. movement, coughing, grimacing or sucking on the endotracheal tube) and were mainly reported in phase II trials in which sugammadex was administered 3–15 minutes after the neuromuscular blocking agent, rather than in phase III trials where sugammadex was administered at the reappearance of T2 or 1–2 PTC. The incidence of anaesthetic

Fig. 5. Tolerability of sugammadex (SUG) compared with neostigmine plus glycopyrrolate (NEO). Incidence of adverse events occurring in >6% of SUG or NEO recipients. Data were pooled from two phase III trials in surgical patients administered SUG 2 or 4 mg/kg, or neostigmine 50 or 70 μg/kg plus glycopyrrolate 10 or 14 μg/kg at the reappearance of the second twitch in the train-of-four stimulation or a post-tetanic count of 1–2 following administration of rocuronium or vecuronium. All neuromuscular drugs were given intravenously.
complications with sugammadex 16 mg/kg was >4-fold higher than that with sugammadex 2 or 4 mg/kg or placebo (9.1% vs 1.5–2% and 1.4%); this may reflect the extremely rapid reversal of neuromuscular blockade with the higher sugammadex doses (see section 4).[38] Unwanted awareness during anaesthesia was uncommon and the relationship of this adverse event to sugammadex is unknown.[35]

Residual or recurrent neuromuscular blockade was uncommon with sugammadex.[38] In a pooled analysis of placebo-controlled trials, residual or recurrent neuromuscular blockade was reported in 1.7% of sugammadex <2–16 mg/kg and in 0.0% of placebo recipients; the majority (20 of 24 cases; 83%) were reported in individuals who received sugammadex at sub-optimal doses of sugammadex at <2 mg/kg.[38] No cases were reported in a pooled analysis of the comparative trials with neostigmine plus glycopyrrolate.[38]

The frequency of hypersensitivity or allergic reactions to sugammadex was low (<1%) in a total of 1926 recipients of sugammadex at various doses up to 32 mg/kg.[38] In phase III trials, adverse events that may reflect a hypersensitivity or allergic reaction (such as contact dermatitis, allergic pruritus, drug hypersensitivity or transfusion reaction) were not considered by the trial investigators to be related to sugammadex.[38] In two large phase I trials (n=62[38] or 83[37]), six volunteers who had received sugammadex 32 mg/kg had symptoms (e.g. skin flushing and rash) consistent with possible hypersensitivity to sugammadex. In another phase I trial (n=13),[38,63] one volunteer who had received 8.4 mg/kg of the scheduled 32 mg/kg sugammadex dose had a probable hypersensitivity reaction and a positive intradermal skin test.

Adverse events with an incidence of >2% in the sugammadex arm and at least twice that of the incidence in the neostigmine plus glycopyrrolate arm include flatulence (5.6% vs 2.4%) and postoperative gastrointestinal disorder (2.2% vs 0.0%).[38] Adverse events in neostigmine plus glycopyrrolate recipients with an incidence at least twice that of sugammadex recipients included dry mouth (8.4% vs 2.2%; figure 5), anxiety (4.8% vs 1.7%) and prolonged neuromuscular blockade (2.4% vs 0.0%).[38] In a single-site report of a multicentre phase III trial,[56] the incidence of post-anaesthetic dry mouth was significantly lower with sugammadex (5%; 1 of 20 patients) than with neostigmine plus glycopyrrolate (85%; 17 of 20) or with edrophonium plus atropine (95%; 19 of 20) [p<0.05 for both].

No abnormalities in laboratory parameters or changes in vital signs were considered to be related to sugammadex[50] or clinically significant;[48,51,57] laboratory parameters and vital signs were generally similar between treatment arms.[50-55,59]

5.2 In Special Patient Populations

In general, the tolerability of sugammadex in younger adult patients was similar to that in elderly[58] or paediatric[49] patients.[38]

Tolerability of sugammadex was generally similar between patients with normal renal function and those with severe renal impairment.[38,48] However, sugammadex is not recommended for use in patients with severe renal impairment (section 6).

Sugammadex was generally well tolerated in surgical patients with cardiac disease (including ischaemic heart disease, chronic heart failure or arrhythmia).[42] There was no statistically significant between-group difference in mean QT interval corrected by Fridericia’s formula between recipients of sugammadex 2 or 4 mg/kg or placebo. However, a serious adverse event of QTc interval prolongation that was considered potentially related to the study medication was reported in three patients with cardiac disease, one patient in each of the sugammadex 2 or 4 mg/kg or placebo groups.[42]

In surgical patients with pulmonary disease (including asthma, chronic obstructive pulmonary disease or bronchitis), sugammadex was generally well tolerated.[59] However, two patients with asthma experienced a serious adverse event of bronchospasm, both following administration of sugammadex 4 mg/kg.[59] One patient who was already extubated at the time of the occurrence of bronchospasm (=3.5 minutes after the
administration of sugammadex) was treated with terbutaline sulfate; the other patient who was not yet extubated, experienced bronchospasm 55 minutes after the administration of sugammadex, received salbutamol (albuterol) via the endotracheal tube.[59]

6. Dosage and Administration

Sugammadex is indicated in the EU to reverse rocuronium- or vecuronium-induced neuromuscular blockade in adult patients or rocuronium-induced neuromuscular blockade in paediatric patients (table V). Sugammadex is also approved in Australia, Iceland, New Zealand and Norway. Sugammadex should be administered by, or with the supervision of, an anaesthetist.[35] Appropriate monitoring of the level of neuromuscular blockade is recommended.[14]

Sugammadex should be given as a single intravenous bolus, delivered within 10 seconds.[35] Should postoperative neuromuscular blockade occur following administration of sugammadex 2 or 4 mg/kg, a further dose of 4 mg/kg is recommended. If a repeat administration of rocuronium or vecuronium is required, the recommended waiting period is 24 hours after administration of sugammadex; however, if neuromuscular blockade is needed before 24 hours, a nonsteroidal agent should be used.[35]

The use of sugammadex in patients with known hypersensitivity to the active drug or any of the excipients is contraindicated, and use in patients with severe renal impairment is not recommended.[33] The local manufacturer’s prescribing information should be consulted for full details of other warnings and precautions, patient monitoring and administration recommendations, use in special patient populations and potential drug-drug interactions.

7. Place of Sugammadex in Anaesthetic Practice

A recent study estimated that 187–281 million major surgical procedures were performed globally in 2004.[68] Given this large estimate, the continued effort to improve surgical outcomes, including the development of better anaesthetic drugs, is of benefit. A major issue in anaesthetic practice is the transition from the paralysed, anaesthetized state to the fully-awake state with normal muscle function.[69] The general consensus is that return to TOF 0.9 or better should be achieved at the end of surgery prior to extubation; however, this does not always occur.[70-72]

The ideal neuromuscular blocking agent should have brief, noncumulative, nondepolarizing neuromuscular action with rapid onset and recovery times, and have no clinically important adverse effects.[9,73] Of the most widely used nondepolarizing agents (the steroid-based agents rocuronium and vecuronium and the benzylisoquinolones atracurium and cisatracurium), rocuronium has the most rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8] Suxamethonium chloride has both a rapid onset of action (<1 minute with 1.2 mg/kg, or <2 minutes with lower doses) and an intermediate duration of action (37 minutes with 0.6 mg/kg).[8]

For over 30 years, the most widely used neuromuscular blockade reversal agents have been the anticholinesterases, of which the most commonly employed is neostigmine.[7,74] These agents act by inhibiting the breakdown of acetylcholine, thus increasing the amount of acetylcholine at the neuromuscular junction; they have no effect on

| Table V. Recommended usage of sugammadex (SUG) in the EU.[35] Consult local prescribing information for full administration details |
|------------------|------------------|------------------|------------------|
| Patient age (y) | Neuromuscular blocking agent | Type of reversal | SUG dose (mg/kg)a |
| ≥18 | ROC or VEC | Routine (moderate) | 2b |
| ≥18 | ROC or VEC | Routine (deep) | 4c |
| ≥18 | ROC | Immediate | 16 |
| 2–17 | ROC | Routine (moderate) | 2 |
| a The most appropriate dose of SUG is dependent on the level of neuromuscular blockade to be reversed and is independent of the anaesthetic regimen. |
| b Recommended if spontaneous recovery has occurred, up to the reappearance of T2 following neuromuscular blockade. |
| c Recommended if recovery has reached at least 1–2 post-tetanic counts following neuromuscular blockade. |

ROC = rocuronium; T2 = the second twitch in the train-of-four stimulation; VEC = vecuronium.
the metabolism or elimination of neuromuscular blocking agents. Major limitations of these drugs include the inability to reverse deep neuromuscular blockade and the need for concurrent administration of anticholinergic agents to minimize adverse effects (section 1). In addition, the duration of action of anticholinesterases may be shorter than the activity of the neuromuscular blocking agent; consequently, residual paralysis may be evident, or paralysis may reappear. In a meta-analysis, postoperative residual neuromuscular blockade after reversal was reported in 11.5–41.3% of patients receiving a single intubating dose of an intermediate-acting nondepolarizing blocking agent. This contributes significantly to postoperative morbidity and mortality (e.g. hypoxaemia or upper airway obstruction); adequate postoperative reversal of neuromuscular blockade is an anaesthesia management factor that may reduce postoperative morbidity and mortality. The efficacy limitations and the undesirable cholinergic effects of both the anticholinesterases and the antimuscarinic agents administered to mitigate cholinergic adverse effects (section 1) mean that this combination of drugs is far from ideal, and some anaesthetists do not routinely employ anticholinergic reversal agents because of these potential limitations.

Sugammadex is the first selective relaxant binding agent to be recommended for use in anaesthetic practice, specifically to reverse the neuromuscular blockade induced by rocuronium or vecuronium; it was first approved in the EU in July 2008. Compared with older reversal agents, sugammadex has a unique mechanism of action in that it inactivates the neuromuscular blocking agent and has a high affinity and specificity for rocuronium and vecuronium (section 2). Because sugammadex is not metabolized, it is associated with few drug interactions (section 2.4 and section 3.2); in addition, sugammadex and the sugammadex-rocuronium complex are relatively quickly eliminated from the body (section 3) because of their water solubility. The stability of the sugammadex-rocuronium complex (section 2.1) means that reoccurrence of neuromuscular blockade due to dissociation is unlikely.

The efficacy of sugammadex has been established in several well designed phase III trials, including special patient populations such as elderly or paediatric patients, or those with renal impairment (section 4). Notably, sugammadex effectively reverses routine doses of rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg), but also deep blockade (e.g. rocuronium 1.2 mg/kg or administration at 1–2 PTC) [section 4]; other reversal agents cannot reverse deep neuromuscular blockade (section 1). Unlike the anticholinesterase reversal agents, reversal of any level of neuromuscular blockade can be initiated with sugammadex even before spontaneous recovery has begun, which may facilitate an earlier resumption of spontaneous breathing. Therefore, sugammadex may be of benefit when a surgical procedure ends prematurely, and the level of neuromuscular blockade (with rocuronium or vecuronium) can be maintained for any duration of time, including deep neuromuscular blockade needed in some surgeries.

The use of sugammadex following rocuronium or vecuronium provides a clear advantage in terms of the speed of neuromuscular blockade reversal when compared with the use of other neuromuscular blockade reversal agents, the reversal of cisatracurium with neostigmine plus glycopyrrolate or spontaneous recovery with suxamethonium chloride (section 4.1). Sugammadex has good efficacy in special patient groups, including elderly and paediatric patients and patients with renal impairment, or cardiac or pulmonary disease (section 4.2). As the elimination of the sugammadex-rocuronium complex in patients with severe renal impairment is significantly delayed (section 3.2), the dialysability of the complex requires further investigation before sugammadex can be considered for use in this population.

Unlike neostigmine, the efficacy of sugammadex in reversing routine rocuronium-induced neuromuscular blockade was not affected by whether propofol-induced anaesthesia was maintained with propofol or sevoflurane (section 2). However, although the effect of different maintenance anaesthesia regimens on the efficacy of sugammadex in reversing deep neuromuscular blockade has not
been directly compared, results from two studies (section 4.1) suggest that sugammadex is effective when administered during deep neuromuscular blockade in patients under sevoflurane maintenance anaesthesia.

The use of suxamethonium chloride in patients with genetic mutations in the butyrylcholinesterase gene is associated with unpredictably prolonged periods of neuromuscular blockade (relaxation duration 12–300 minutes). If the use of sugammadex could predictably reverse neuromuscular blockade, the potential adverse effects of prolonged neuromuscular blockade could be avoided and the time patients need to be held in the operating theatre because of incomplete neuromuscular blockade reversal could be reduced. However, in a small number of patients, the time to reverse rocuronium-induced neuromuscular blockade with sugammadex is longer than in the majority of other patients, an observation tending to occur in studies when administration of sugammadex was based on the time (15 minutes) after the last dose of rocuronium and not based on the level of neuromuscular blockade. For example, in a dose-finding study, the time to reach TOF 0.9 ranged from 0.9 to 16.6 minutes versus a mean of 4.7 minutes in five patients who received sugammadex 16 mg/kg (the maximum recommended dose; section 6) 15 minutes after rocuronium 1.2 mg/kg. In an observational study in which 169 evaluable patients received sugammadex 4 mg/kg at least 15 minutes after the last dose of rocuronium (0.6 mg/kg for induction or 0.15 mg/kg for maintenance as required), although most (=87%) patients achieved TOF 0.9 in <5 minutes, 4% of patients achieved TOF 0.9 only after 5.0–22.3 minutes. In the latter study, the twitch response on TOF nerve stimulation varied from no response (i.e. no twitches) to three twitches at the time of sugammadex administration.

Despite a better tolerability profile, rocuronium is recommended as a second-line agent to suxamethonium chloride for use in rapid-sequence intubation because of its longer duration of action. The use of sugammadex in combination with rocuronium could theoretically shorten the period of action, although their use in this indication has not been evaluated. Sugammadex can potentially be used to rapidly reverse rocuronium in a ‘cannot intubate, cannot ventilate’ situation, however, because this situation cannot be studied ethically, clinical experience of sugammadex in this situation may help to address its use as a ‘rescue’ reversal agent. Although residual neuromuscular blockade with recommended use of sugammadex in postoperative care is unlikely (section 5.1), neuromuscular monitoring is still needed despite the extensive and rapid reversal, as it would help to determine the depth of neuromuscular blockade and therefore the sugammadex dose required for reversal.

As with all new pharmacological agents, safety is of paramount importance. Sugammadex is well tolerated in adult surgical patients and in special patient populations, and has a generally similar tolerability profile to that of placebo or neostigmine plus glycopyrrolate (section 5.1). The most commonly reported adverse events (procedural pain, nausea and vomiting) in all study arms are typical of patients undergoing surgical procedures. The use of sugammadex minimizes the risk of adverse events commonly associated with neostigmine plus glycopyrrolate or edrophonium plus atropine, such as dry mouth (section 5.1). In addition, sugammadex does not appear to have adverse cardiovascular effects (section 2), including in patients with underlying cardiac disease (section 5.2). Importantly, residual neuromuscular blockade was infrequent with recommended doses of sugammadex.

There are some limitations associated with the use of sugammadex. In the event that re paralysis is needed, rocuronium or vecuronium should not be given within 24 hours of sugammadex administration (nonsteroidal neuromuscular blocking agents are recommended in this situation; section 6). Sugammadex has no effect on nonsteroidal neuromuscular blocking agents and other agents (e.g. neostigmine) are required for their reversal. The ease of reversing even deep neuromuscular blockade with the use of sugammadex may potentially lead to the use...
of higher dosages of neuromuscular blocking agents; as paralysis can mask inadequate levels of anaesthesia and analgesia, other means of assessing the extent of analgesia and anaesthesia may be needed.\[14\]

Although a preliminary model of cost savings was favourable with the use of sugammadex in terms of reducing the postoperative time spent in the operating room,\[88\] this was a US-based model and may not apply in other countries or healthcare systems. In addition, this model did not include the acquisition cost of sugammadex. Therefore, pharmacoeconomic analyses based on hospital and acquisition costs in other countries would be of interest.

Other issues relating to the use of sugammadex remain to be elucidated. The incidence of hypersensitivity is available only among \( \approx 2000 \) clinical trial participants (section 5.1)\[38\] and requires further investigation. It should be noted that the FDA not-approvable letter issued in August 2008 was based on the potential for hypersensitivity/allergic reactions to sugammadex, rather than a lack of efficacy.\[89\] The majority of individuals enrolled in the sugammadex clinical trials had relatively good health (ASA classes I–III) [section 5]; it would be of benefit to evaluate the efficacy and tolerability of sugammadex in patients with poorer health (i.e. ASA class IV). Studies of sugammadex in patients with neuromuscular disease (e.g. myasthenia gravis) would also be of interest.\[69\] The tolerability of rocuronium plus sugammadex compared with suxamethonium chloride in the greater population is also needed.\[7\]

In conclusion, in clinical trials in adult surgical patients with relatively good health, sugammadex at recommended doses provided rapid reversal of rocuronium- or vecuronium-induced neuromuscular blockade with a low incidence of residual or recurrent neuromuscular blockade and was generally well tolerated. In paediatric patients, sugammadex effectively reversed rocuronium-induced neuromuscular blockade and was generally well tolerated. Several factors associated with the use of sugammadex have yet to be determined, such as the efficacy and safety in patients with poorer health or in those with neuromuscular disorders, the incidence of infrequent adverse events in larger patient populations and the cost effectiveness of the drug relative to existing reversal agents. Nevertheless, sugammadex is a useful addition to the reversal agents commonly employed in anaesthetic practice.

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