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Original Contribution

# Incidence of hypersensitivity and anaphylaxis with sugammadex

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ABSTRACT

*Study objective:* To evaluate the incidence of hypersensitivity and anaphylaxis after administration of sugammadex.
*Design:* Retrospective analysis.
*Setting:* Sugammadex clinical development program and post-marketing experience.
*Patients:* Surgical patients and healthy volunteers who received sugammadex or placebo/comparator with anesthesia and/or neuromuscular blockade (NMB).
*Interventions:* Sugammadex administered as 2.0 mg/kg at reappearance of the second twitch, 4.0 mg/kg at 1–2 post-tetanic count, or 16.0 mg/kg at 3 min after rocuronium 1.2 mg/kg.
*Measurements:* Three analytical methods were used: 1) automated MedDRA queries; 2) searches of adverse events (AEs) consistent with treatment-related hypersensitivity reactions as diagnosed by the investigator; and 3) a retrospective adjudication of AEs suggestive of hypersensitivity by a blinded, independent adjudication committee (AC). In addition, a search of all post-marketing reports of events of hypersensitivity was performed, and events were retrospectively adjudicated by an independent AC. Anaphylaxis was determined according to Sampson Criterion 1.
*Main results:* The pooled dataset included 3519 unique subjects who received sugammadex and 544 who received placebo. The automated MedDRA query method showed no apparent increase in hypersensitivity or anaphylaxis with sugammadex as compared to placebo or neostigmine. Similarly, there was a low overall incidence of AEs of treatment-related hypersensitivity (< 1%), with no differences between sugammadex and placebo or neostigmine. Finally, the retrospective adjudication of AEs suggestive of hypersensitivity showed a low incidence of hypersensitivity (0.56% and 0.21% for sugammadex 2 mg/kg and 4 mg/kg, respectively), with an incidence similar to subjects who received placebo (0.55%). There were no confirmed cases of anaphylaxis in the pooled studies. During post-marketing use, spontaneous reports of anaphylaxis occurred with approximately 0.01% of sugammadex doses.
*Conclusions:* Subjects who received sugammadex with general anesthesia and/or NMB had a low overall incidence of hypersensitivity, with no apparent increase in hypersensitivity or anaphylaxis with sugammadex as compared to placebo or neostigmine.

## 1. Introduction

Sugammadex is a selective relaxant-binding agent that provides rapid reversal of moderate or deep neuromuscular blockade (NMB) [1–6]. Following administration of sugammadex in the presence of the NMB agent (NMBA), a sugammadex-NMBA complex is formed that prevents binding of the NMBA to the nicotinic receptors on the postsynaptic muscle membrane, resulting in reversal of NMB. Sugammadex is indicated for reversal of moderate NMB (2 mg/kg) and deep NMB (4 mg/kg) induced by rocuronium or vecuronium. The sugammadex dose of 16 mg/kg is recommended only in the case of an urgent or emergent need to reverse NMB following administration of rocuronium [7].

Sugammadex is considered generally safe and well-tolerated, however, dose-related hypersensitivity reactions have been reported with its use [8–15]. A retrospective analysis of data from clinical trials conducted in healthy, non-anesthetized volunteers who received sugammadex (0.5–96 mg/kg) demonstrated suspected signs or symptoms

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of hypersensitivity (rash, flushing, feeling of warmth in arms and legs, difficulty breathing, nausea, stomach discomfort, palpitations, tachycardia, paresthesia, and visual disturbance) in 6 subjects, which occurred soon after bolus administration of sugammadex at doses ranging from 8 to 32 mg/kg [3,4]. These symptoms were not serious or severe in intensity, and were short-lasting and self-limiting. A repeat-dose, placebo-controlled study conducted in a healthy, non-anesthetized population (N = 448) detected signs of hypersensitivity in 7 subjects (4.7%) who received sugammadex 16 mg/kg, 1 subject (0.7%) who received sugammadex 4 mg/kg, and no subjects who received placebo. In this study, 3 subjects met the Sampson and Brighton anaphylaxis criteria (level 1, N = 1; level 2, N = 2) [16,17]; however, protocol deviations that may have compromised study blinding in a subset of subjects were noted following study completion. Subsequently, a multicenter, double-blind study [18] that evaluated the incidence of hypersensitivity and anaphylaxis after repeated, single-dose administration of sugammadex among 375 non-anesthetized adults showed that both the 4 mg/kg (N = 151) and 16 mg/kg (N = 148) doses were associated with numerically higher incidences (5.3% and 8.1%, respectively) of hypersensitivity than placebo (N = 76). A single case of anaphylaxis occurred in the 16 mg/kg treatment group. There was no evidence of apparent sensitization with repeated sugammadex administration.

The present pooled analysis was performed to further characterize the potential risk of hypersensitivity and anaphylaxis following exposure to sugammadex among surgical patients under general anesthesia requiring NMB and healthy volunteers who received sugammadex or placebo together with anesthesia and/or NMB across the Phase 1–3 studies in the sugammadex clinical development program. In addition, post-marketing reports of events of hypersensitivity and anaphylaxis were identified and adjudicated.

## 2. Methods

### 2.1. Study design

Data were pooled across all Phase 1–3 sugammadex clinical studies, comprising 42 trials, including 6 Phase 1 trials, 12 Phase 2 trials, and 23 Phase 3 trials; in addition, 1 Phase 5 trial assessing the effect of sugammadex and neostigmine on incidence of residual blockade was included for completeness (Supplemental Fig. 1). Adult surgical patients and healthy volunteers from any trial in which sugammadex 2, 4, and/or 16 mg/kg doses, placebo and/or comparator was administered together with anesthesia and/or NMB were included. In addition to the overall Phase 1 to 3 pooled population, two subsets of interest were defined: 1) sugammadex compared to placebo (pooled placebo-controlled subgroup) and 2) sugammadex compared to neostigmine (pooled neostigmine-controlled subgroup).

All study protocols had been reviewed and approved by the appropriate Institutional Review Boards or Independent Ethics Committees. All clinical trial subjects had provided written informed consent before the initiation of any study procedure.

### 2.2. Subjects and procedures

Subjects were eligible for inclusion in the base clinical studies if they were ≥ 18 years of age, American Society of Anesthesiologists (ASA) Class 1–3, and scheduled to undergo surgery under general anesthesia requiring NMB. In general, the exclusion criteria included disorders impairing neuromuscular transmission, use of medication known to interfere with NMBAs, significant renal dysfunction, a history of malignant hyperthermia, and allergy to medication used during general anesthesia. Subjects who were pregnant, breast feeding, or of childbearing potential and not using an adequate method of contraception were also excluded.

The anesthesia regimen in the studies was propofol for induction and propofol or sevoflurane for maintenance. Subjects received rocuronium (0.6–1.2 mg/kg) or vecuronium (0.1 mg/kg) for NMB, with additional maintenance doses, as required. Comparators were placebo or neostigmine (50–70 μg/kg), which was given with the muscarinic antagonists glycopyrrolate 10 μg/kg or atropine 10–20 μg/kg. Across the studies (except for those exploring the dose range), sugammadex was administered according to 3 recommended administration schedules: 2.0 mg/kg at reappearance of the second twitch (T2) to Train-of-Four (TOF) stimulation, 4.0 mg/kg at 1–2 post-tetanic count (PTC), or 16.0 mg/kg at 3 min after rocuronium 1.2 mg/kg. Neuromuscular monitoring was performed using the TOF-Watch® SX (Organon Ireland Ltd., formerly a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland).

### 2.3. Hypersensitivity assessment

Hypersensitivity was defined as objective symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by non-hypersensitive persons. Anaphylaxis was defined according to Sampson (Criterion 1) [16]: acute onset of an illness (from minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following events: respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia); or reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

Three methods were used to assess hypersensitivity/anaphylaxis in the pooled clinical trial database: 1) automated Medical Dictionary for Regulatory Activities (MedDRA) [19] queries; 2) searches of adverse events (AEs) suggestive of hypersensitivity as diagnosed by the investigator and considered treatment-related in the opinion of the investigator; and 3) a retrospective adjudication of AEs suggestive of hypersensitivity by an independent adjudication committee (AC; see Appendix A for the list of hypersensitivity symptoms referred to the AC). In addition, a search of all post-marketing reports of events of hypersensitivity and anaphylaxis was performed, and events were adjudicated by an independent AC.

#### 2.3.1. Automated MedDRA queries

For the automated MedDRA query approach, the Standardized MedDRA Query (SMQ) for “Hypersensitivity” was used to identify clinical trial subjects who may have experienced a hypersensitivity reaction. The queries used terms from the “narrow” and “broad” searches, as defined within the SMQ. The “narrow” term search was used to identify events that are highly likely to represent the condition of interest, and the “broad” term search included identification of all possible events related to hypersensitivity and also captured terms from the “narrow” search.

In addition to “Hypersensitivity”, the SMQ, “Anaphylactic reaction” was used to identify subjects who may have experienced an anaphylactic reaction, using terms from the “narrow”, “broad” and “algorithmic” searches. Similar to the “Hypersensitivity” SMQ, the “narrow” search included terms that are most indicative of an anaphylactic reaction and the “broad” search included all possible anaphylactic events and also captured terms from the “narrow” search. The “algorithmic” search accounted for the fact that anaphylaxis typically involves a combination of reactions and, therefore, included the following three categories of “broad” terms: upper airway/respiratory, angioedema/urticaria/pruritus/flush, and cardiovascular/hypotension. For the “algorithmic” search, a subject was required to either experience an event from the “narrow” search or experience at least two events from two different categories from the “broad” search.

#### 2.3.2. Adverse events of treatment-related hypersensitivity per the investigator

For the second approach, AEs of hypersensitivity or anaphylaxis