

Resubmission

sugammadex 100mg/mL (1mL, 2mL, 5mL) solution for injection (Bridion®)
SMC No. (527/09)

Merck, Sharp & Dohme Limited

08 February 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

sugammadex (Bridion®) is accepted for restricted use within NHS Scotland for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults and rocuronium in children and adolescents.

Indication under review: Reversal of neuromuscular blockade induced by rocuronium or vecuronium. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents. This resubmission is for the part of the indication relating to routine reversal of neuromuscular blockade.

SMC restriction: only for use in the routine reversal setting in high-risk patients (e.g. morbid obesity, significant respiratory disease or reduced respiratory reserve, significant coronary disease, major abdominal/chest surgery) or where prompt reversal of neuromuscular block is required.

Sugammadex, when administered after rocuronium or vecuronium, has been shown to provide more rapid reversal of moderate and profound neuromuscular blockade than an anti-cholinesterase comparator.

Sugammadex is significantly more expensive than conventional treatments used to reverse neuromuscular blockade.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Published 11 March 2013

Indication

Reversal of neuromuscular blockade induced by rocuronium or vecuronium. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents.

Dosing Information

Sugammadex should only be administered by, or under the supervision of an anaesthetist. The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed.

Routine reversal [adults]

A dose of 4mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 3 minutes.

A dose of 2mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 2 minutes.

Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the T_4/T_1 ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade.

Children and adolescents

For routine reversal of rocuronium induced blockade at reappearance of T_2 in children and adolescents (2 to 17 years) 2mg/kg sugammadex is recommended. Other routine reversal situations have not been investigated and are therefore not recommended until further data become available.

Product availability date

3 November 2008

Summary of evidence on comparative efficacy

Sugammadex is a γ -cyclodextrin, the first selective relaxant binding agent for the non-depolarising neuromuscular blocking agents, rocuronium and vecuronium. It forms an inclusion complex with the neuromuscular blocking agent, encapsulating it, reducing the amount of free neuromuscular blocking agents available to bind to receptors in the neuromuscular junction and resulting in reversal of blockade.¹

Sugammadex has a marketing authorisation for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population, it is only licensed for routine reversal of rocuronium-induced blockade. SMC previously considered sugammadex

within its licensed indication in 2009 and accepted it for restricted use for the immediate reversal of rocuronium-induced neuromuscular blockade in adults only. It was not recommended for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults and rocuronium in children or adolescents. In this resubmission, the use of sugammadex for the routine reversal of moderate (shallow) or profound (deep) rocuronium- or vecuronium-induced neuromuscular blockade in the elective surgery setting is being considered. Sugammadex is available in two vial sizes, 2mL and 5mL. The submitting company has requested that SMC considers the 2mL vial size only as the 5mL preparation is used in the emergency setting (for which SMC has already issued accepted advice). In the routine reversal of profound block setting, costing has been undertaken only for the 2mL vial size. This is based on experience in England, which shows that it is common practice to use two 2mL vials rather than a single 5mL vial in this scenario.

Three pivotal, phase III studies have been conducted: two in the routine reversal of shallow neuromuscular block (AURORA and CRYSTAL) and one in the reversal of profound neuromuscular block (SIGNAL).²⁻⁶ The studies were all unblinded (except for the safety assessor), randomised, active-comparator studies. The studies recruited adults scheduled for a surgical procedure in the supine position with general anaesthesia, and with an American Society of Anaesthesiologists (ASA) classification of physical status I to III (in the shallow neuromuscular block studies) and IV (in the profound neuromuscular block study). The primary outcome in the intention-to-treat (ITT) population was the time from the start of administration of sugammadex or neostigmine with glycopyrrolate to recovery of the T_4/T_1 ratio to 0.9 (a sufficient recovery and thus adequate respiration), where T_1 is the amplitude of the first twitch (first response to stimulation) and T_4 is the fourth twitch; with a complete recovery when the ratio is approximately 0.9. Due to a skewed distribution, the logarithm of the recovery time was taken as the response variable and summarised using the geometric mean.

In the AURORA study, patients were randomised to either rocuronium 0.6mg/kg (plus maintenance doses) or vecuronium 0.1mg/kg (plus maintenance doses).^{2,3} After the last dose of rocuronium or vecuronium, at reappearance of T_2 , patients were randomised to sugammadex 2mg/kg or neostigmine 50micrograms/kg with glycopyrrolate 10micrograms/kg. In the rocuronium group, the geometric mean time from administration of sugammadex (n=48) or neostigmine (n=48) to recovery of the T_4/T_1 ratio to 0.9, was significantly shorter in the sugammadex group (1.5 minutes versus 18.6 minutes). Similarly, in the vecuronium group, the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was significantly shorter with sugammadex (n=48) compared with neostigmine (n=45); (2.7 minutes versus 17.9 minutes).

In the CRYSTAL study, patients were randomised to rocuronium 0.6mg/kg followed by reversal with sugammadex 2mg/kg (n=34), or cisatracurium 0.15mg/kg followed by reversal with neostigmine 50micrograms/kg plus glycopyrrolate 10micrograms/kg (n=39).⁴ Reversal agents were administered after the last dose of neuromuscular blocking agent, at reappearance of T_2 . The geometric mean time from administration of the reversal agent to recovery of the T_4/T_1 ratio to 0.9 was 1.9 minutes in the sugammadex group and 9.0 minutes in the neostigmine group. This difference in recovery times was statistically significant.

In the SIGNAL study, patients were randomised to rocuronium or vecuronium (doses as for AURORA study).^{5,6} After the last dose of rocuronium or vecuronium, patients were randomised to sugammadex 4mg/kg or neostigmine 70micrograms/kg with glycopyrrolate 14microgram/kg which were commenced at reappearance of 1 to 2 post-tetanic counts (PTC). In the rocuronium group, the geometric mean time from administration of sugammadex (n=37) or neostigmine (n=37) to recovery of the T_4/T_1 ratio to 0.9 was significantly shorter with sugammadex (2.9

minutes versus 50.4 minutes). Similarly, in the vecuronium group, the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was significantly shorter with sugammadex (n=47) compared with neostigmine (n=36); (4.5 minutes versus 66.2 minutes).

In a dose-ranging study, following administration of rocuronium 0.6mg/kg, 94 patients (including infants, children, adolescents and adults) received a single, bolus, intravenous dose of sugammadex (0.5, 1, 2, or 4mg/kg) or placebo at the reappearance of T_2 .⁷ In children, adolescents and adults a clear dose-response relationship was found, but not for infants. The recovery time was markedly decreased in paediatric subjects.

Summary of evidence on comparative safety

For licensing, safety data have been collected from 29 studies (including 14 phase II and 10 phase III studies) giving a safety database of over 1,700 patients. Pooled analyses indicated that sugammadex was generally well tolerated and the most commonly reported adverse events were routinely managed events typical of a surgical/post-surgical population.¹

In the phase III studies, the safety assessor was blinded to treatment allocation and the adverse event profile of rocuronium/vecuronium plus sugammadex was similar to the comparators. Generally, treatment-related adverse events were mild or moderate in intensity and occurred in small numbers of patients. In the sugammadex group they included nausea, chills, tremor and procedural hypertension. In paediatric patients, sugammadex was well tolerated; however, the number of patients treated was small.

The published reports from two pivotal studies recorded no clinical evidence of residual neuromuscular block or reoccurrence of neuromuscular block.^{2,3,5,6} The summary of product characteristics for sugammadex notes that in clinical trials recurrence of neuromuscular blockade was reported mainly when sub-optimal doses (in dose finding studies) were administered. Furthermore, the European Medicines Agency (EMA) considered the risk of reoccurrence at licensed doses to be very low.¹

A number of safety issues were identified requiring continued pharmacovigilance or post-authorisation commitment. A total of seven patients in clinical trials were identified with clinical symptoms which may have been indicative for hypersensitivity to sugammadex. At present, there is no suggestion from clinical data or from the literature of cross-sensitivity with other cyclodextrins or with antibiotics with structural similarity to sugammadex. The possibility of drug hypersensitivity reactions is included in the updated summary of product characteristics (SPC) following a variation filed with the EMA in 2010.

Summary of clinical effectiveness issues

This resubmission relates to sugammadex for the routine reversal of moderate (shallow) or profound (deep) rocuronium- or vecuronium-induced neuromuscular blockade in the elective surgery setting. The submitting company has requested that SMC considers the 2mL vial size only. In the pivotal clinical studies, sugammadex, when administered after rocuronium or vecuronium, provided a more rapid reversal of shallow and profound neuromuscular blockade than neostigmine with glycopyrrolate. Also sugammadex when administered after rocuronium was superior to neostigmine for reversal of cisatracurium neuromuscular blockade. The

evidence base in patients with poorer physical status is limited. The majority of patients had ASA I and II physical status, and no patients with ASA IV physical status were recruited to the pivotal studies.

The EMA commented that when reversal of profound neuromuscular blockade is required, the use of sugammadex would be of clinical value because it produces rapid recovery of neuromuscular function. However, the EMA noted that reversal of this level of neuromuscular block is not routine.

Sugammadex has a novel mechanism of action which does not result in stimulation of the cholinergic nervous system, thereby avoiding the undesirable autonomic nervous system side effects of the anticholinesterases currently used to reverse the effects of non-depolarising neuromuscular agents routinely used in elective surgery. However, sugammadex is only licensed for reversal of neuromuscular blockade induced by rocuronium and vecuronium and is not effective for reversal of neuromuscular blockade induced by cisatracurium or atracurium. How the introduction of sugammadex might influence the choice of neuromuscular blocking agent used routinely is not known.

The relevant comparator for the positioning proposed by the company is neostigmine with glycopyrrolate when used for reversal of rocuronium, vecuronium, atracurium or cisatracurium induced neuromuscular blockade, or no reversal treatment. There are no direct comparative data versus neostigmine in atracurium-induced neuromuscular blockade and an indirect comparison was not provided because of the absence of linkages. Therefore, the comparative efficacy and safety of sugammadex reversal of rocuronium/vecuronium-induced neuromuscular blockade versus neostigmine reversal of atracurium-induced neuromuscular blockade is not known.

There was lack of consensus from SMC clinical experts regarding the place in therapy of sugammadex. However, most considered that sugammadex may be useful in situations where there is a clinical safety concern (e.g. obese patients, respiratory/cardiac issues) and when reversal of profound neuromuscular block is required. Some SMC clinical experts expressed concerns about the use of sugammadex for routine cases where the use of existing reversal agents is adequate as it is significantly more expensive than conventional treatments used to reverse neuromuscular blockade. Area Drug and Therapeutics Committees may therefore wish to consider the development of a local protocol to ensure its cost-effective use.

Summary of comparative health economic evidence

The submitting company presented a cost-effectiveness analysis comparing sugammadex with neostigmine for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. Sugammadex is only licensed for the reversal of rocuronium or vecuronium-induced neuromuscular blockade. However, the company acknowledged that atracurium is the most widely used blocking agent and therefore a comparison with atracurium plus neostigmine was also provided.

The economic analysis focused on the use of sugammadex in the following non-emergency scenarios:

- Routine reversal of moderate neuromuscular blockade (using sugammadex 2mg/kg) induced by either rocuronium or vecuronium in an elective surgery scenario.

- Routine reversal of profound neuromuscular blockade (using sugammadex 4mg/kg) induced by either rocuronium or vecuronium in an elective surgery scenario.

A decision-tree model was used with three health states: death, normal recovery (with or without postoperative nausea and vomiting) and prolonged recovery (with associated adverse events including hypoxaemia, and aspiration). The model followed patients over a short-term time horizon until they recovered from surgery and were discharged. The health outcome measure was the proportion of cases of prolonged recovery prevented based on a systematic review of the literature. The mean time to recovery to a T_4/T_1 ratio of 0.9 for each treatment was also included based on the studies identified from a separate published systematic review. The model included the costs of patients recovering in theatre and it was assumed that any reduction in recovery time to a T_4/T_1 ratio of 0.9 with sugammadex would lead to resource use savings on the basis that the time saved would be put to use by staff, or more surgical procedures could be performed as a result. The costs of treating post-operative nausea and vomiting and aspiration pneumonia were also included.

In the moderate block scenario, the submitting company estimated that sugammadex was the dominant treatment for the reversal of moderate block induced by rocuronium or vecuronium i.e. sugammadex was estimated to prevent more cases of prolonged recovery at lower cost.

Blocker + reversal agent	Proportion of cases of prolonged recovery prevented	Incremental cost	Incremental cost-effectiveness ratio (ICER)
Rocuronium + sugammadex versus:			
Rocuronium + neostigmine	0.24	-£288	Dominant
Vecuronium + neostigmine	0.24	-£354	Dominant
Atracurium + neostigmine	0.29	-£51	Dominant
Vecuronium + sugammadex versus:			
Rocuronium + neostigmine	0.24	-£278	Dominant
Vecuronium + neostigmine	0.24	-£344	Dominant
Atracurium + neostigmine	0.29	-£41	Dominant

In the profound block scenario, the submitting company estimated that sugammadex was the dominant treatment for the reversal of profound block, except in the comparisons with atracurium plus neostigmine where sugammadex was estimated to be more expensive but also more effective.

Blocker + reversal agent	Proportion of cases of prolonged recovery prevented	Incremental cost	ICER
Rocuronium + sugammadex versus:			
Rocuronium + neostigmine	0.24	-£821	Dominant
Vecuronium + neostigmine	0.24	-£1,196	Dominant
Atracurium + neostigmine	0.29	£31	£107
Vecuronium + sugammadex versus:			
Rocuronium + neostigmine	0.24	-£810	Dominant
Vecuronium + neostigmine	0.24	-£827	Dominant
Atracurium + neostigmine	0.29	£43	£148

The following weaknesses were identified:

- The key to offsetting the increased drug cost of sugammadex was the assumption that a reduction in the time to recovery to a T_4/T_1 ratio of 0.9 would lead to a reduction in theatre time. SMC clinical experts have indicated this assumption may not be appropriate as other factors can influence the time patients spend in theatre. However, some sensitivity analysis was provided where the cost per minute of theatre time was reduced from £14 in the base case to £9. This indicated that sugammadex could still be cost-saving in some scenarios when theatre time is valued at a lower cost to take account of this uncertainty.
- There were some weaknesses with the clinical data used in the model. In particular, no direct trial data or formal indirect comparison were available for the comparison with atracurium plus neostigmine. In addition, SMC clinical experts commented that the rates of prolonged recovery used in the model were not reflective of their experience of using neostigmine in practice.
- The place of sugammadex in therapy is uncertain as SMC clinical experts do not consider it appropriate to use sugammadex in the wider elective surgery population. However, it was acknowledged that it would be beneficial to use sugammadex in certain high-risk patient groups.

Despite these weaknesses, the economic case was considered demonstrated in a restricted population of high-risk patient groups or when reversal of profound neuromuscular block is required.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

The most commonly used agent to reverse non-depolarising neuromuscular blockade is the anti-cholinesterase neostigmine, commonly administered with the anticholinergic agent glycopyrrolate.

Cost of relevant comparators

Drug	Dose Regimen	Cost per treatment (£)
Sugammadex	2 to 4mg/kg intravenous injection	60 to 119
Neostigmine	50 to 70micrograms/kg intravenous injection	1
Neostigmine + glycopyrrolate	50micrograms/kg + 10micrograms/kg intravenous injection	2 to 3

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29/11/12 and MIMs (<http://www.mims.co.uk>) on 4/12/12. Costs are based on an adult weighing 70kg.

Additional information: budget impact

Profound Block

The submitting company estimated the population eligible for treatment to be 19,995 in year 1 rising to 20,431 in year 5, with an estimated uptake rate of 7.5% in year 1 and 23.10% in year 5. The gross impact on the medicines budget was estimated to be £179k in year 1 and £563k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £177k in year 1 and £558k in year 5.

Moderate Block

The submitting company estimated the population eligible for treatment to be 29,993 in year 1 rising to 30,646 in year 5, with an estimated uptake rate of 7.5% in year 1 and 23.10% in year 5. The gross impact on the medicines budget was estimated to be £134k in year 1 and £422k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £132k in year 1 and £415k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. European Medicines Agency. European Public Assessment Report for sugammadex (Bridion®). EMEA/CHMP/317523/2008. Accessed on 13/11/12. www.emea.europa.eu
2. Blobner M, Eriksson LI, Scholz J, et al. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: Results of a randomised, controlled trial. European Journal of Anaesthesiology 2010 Oct;27(10):874-81.
3. Khuenl-Brady KS, Wattwil M, Vanacker BF, et al. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. Anesthesia and Analgesia 2010;110(1):64-73.
4. Flockton EA, Mastronardi P, Hunter JM, et al. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. British Journal of Anaesthesia 2008 May;100(5):622-30.
5. Jones RK, Caldwell JE, Brull SJ, et al.. Reversal of profound rocuronium-induced blockade with sugammadex: A randomized comparison with neostigmine. Anesthesiology 2008 Nov;109(5):816-24.
6. Lemmens HJM, El Orbany MI, Berry J, et al. Reversal of profound vecuronium-induced neuromuscular block under sevoflurane anesthesia: Sugammadex versus neostigmine. BMC Anesthesiology 2010 Sep 1;10.
7. Plaud Bt, Meretoja O, Hofmockel R, et al. Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. Anesthesiology 2009;110(2):284-94.

This assessment is based on data submitted by the applicant company up to and including 11 January 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.