sugammadex 100mg/ml solution for injection (Bridion®) No.(527/09)
Schering-Plough

09 January 2009

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 full submission

sugammadex (Bridion®) is accepted for restricted use within NHS Scotland for the immediate reversal of rocuronium-induced neuromuscular blockade.

Sugammadex, when administered after rocuronium or vecuronium, has been shown to provide more rapid reversal of neuromuscular blockade than an anticholinesterase comparator and, when administered with rocuronium in the rapid sequence induction setting, gave a faster mean recovery time than using a depolarising neuromuscular blocking comparator. Sugammadex is accepted for restricted use in the immediate reversal of rocuronium-induced neuromuscular blockade in adults only.

Sugammadex is not recommended for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults, children and adolescents as the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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

Routine reversal (in adults, adolescents and children (2 to 17years)
Recommended dose: 2mg/kg sugammadex if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade.

Routine reversal (in adults only)
Recommended dose: 4mg/kg sugammadex if recovery has reached at least 1 - 2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade.

Immediate reversal of rocuronium-induced blockade (in adults only)
Recommended dose: 16mg/kg sugammadex for immediate reversal following administration of rocuronium. There is no data to recommend the use of sugammadex for immediate reversal following vecuronium induced blockade.

Sugammadex should only be administered by, or under the supervision of, an anaesthetist.

Product availability date

3 November 2008

Summary of evidence on comparative efficacy

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

There were four pivotal, phase lll studies in three different settings in anaesthetics; routine reversal of shallow neuromuscular block, reversal of profound neuromuscular block, and immediate reversal (situations requiring rapid sequence induction [e.g. emergency surgery]). The studies were all unblinded (except for the safety assessor), randomised, active comparator studies.

The studies that investigated shallow and profound neuromuscular blockade recruited adults with an American Society of Anaesthesiologists (ASA) classification of physical status I to IV who were scheduled for a surgical procedure in the supine position with general anaesthesia.

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 T_4/T_1 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 one of two studies investigating reversal of shallow neuromuscular block, patients were randomised to either rocuronium 0.6mg/kg (plus maintenance doses) or vecuronium 0.1mg/kg (plus maintenance doses). After the last dose of rocuronium or vecuronium, at reappearance of T_2, patients were randomised to either sugammadex 2mg/kg or neostigmine 50micrograms/kg with glycopyrrolate. 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 minute: 29 seconds versus 18 minutes: 30 seconds. 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 minutes: 48 seconds versus 16 minutes: 48 seconds.

In the other study, patients were randomised to rocuronium 0.6mg/kg (n=34) or cisatracurium 0.15mg/kg (n=39). After the last dose of neuromuscular blocking agent, at reappearance of T_2, sugammadex 2mg/kg was administered to rocuronium patients, and neostigmine 50micrograms/kg with glycopyrrolate was administered to cisatracurium patients. The geometric mean time from administration of sugammadex in the rocuronium group to recovery of the T_4/T_1 ratio to 0.9 was 2 minutes: 2 seconds and from the administration of neostigmine in the cisatracurium group to recovery of the T_4/T_1 ratio to 0.9 was 8 minutes: 46 seconds. This difference in recovery times was statistically significant.

In a study to investigate reversal of profound neuromuscular block (1 - 2 post-tetanic counts (PTCs)), patients were randomised to one of four treatment groups: rocuronium (intubating dose 0.6mg/kg plus maintenance) followed by reversal with either sugammadex or neostigmine and vecuronium (intubating dose 0.1mg/kg plus maintenance) followed by reversal with either sugammadex or neostigmine. After the last dose of rocuronium or vecuronium, patients had their neuromuscular block reversed at reappearance of 1-2 PTCs with a single bolus dose of either sugammadex 4mg/kg or neostigmine 70micrograms/kg plus glycopyrrolate 14micrograms/kg, according to their randomised treatment group. In the rocuronium group, the geometric mean time from administration of sugammadex (n=37) or neostigmine (n=38) to recovery of the T_4/T_1 ratio to 0.9 was significantly shorter with sugammadex, 2 minutes: 52 seconds versus 50 minutes: 22 seconds. 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=46) compared with neostigmine (n=36), 4 minutes: 28 seconds versus 66 minutes: 12 seconds. The reversal of this level of neuromuscular block is not routine as to relax a patient to a neuromuscular block of 1 - 2 PTCs would be unusual in clinical practice.

In the immediate reversal study, suxamethonium was compared with rocuronium plus sugammadex. Patients were between 18 and 65 years of age, ASA Class I or II and scheduled to undergo a surgical procedure in the supine position under general anaesthesia requiring a short duration of neuromuscular relaxation requiring endotracheal intubation, and with a body mass index of <30. In rapid sequence induction, suxamethonium is used to facilitate intubation, as it has a rapid onset and brief duration of action with spontaneous recovery. Rapid reversal of rocuronium with sugammadex may offer an alternative treatment in this situation.

Following induction of anaesthesia, patients in the rocuronium group (n=55) received an intubation dose of rocuronium 1.2mg/kg followed by reversal of neuromuscular blockade with sugammadex 16mg/kg three minutes after the start of rocuronium administration. Patients in the suxamethonium group (n=55) received an intubation dose of suxamethonium 1mg/kg and were allowed to recover spontaneously from neuromuscular blockade. The primary outcome was the initiation of treatment with either rocuronium or suxamethonium to recovery of T_1 to 10%. This was significantly faster in the rocuronium plus sugammadex group than the suxamethonium group, 4 minutes: 22 seconds versus 7 minutes: 4 seconds.

In a dose-ranging study, following administration of rocuronium 0.6mg/kg, 120 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. It was concluded that for 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

Safety data has been collected from 29 trials (including 14 phase II and 10 phase III studies) giving a safety database of 1,713 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. The most commonly reported adverse events were procedural pain, injection site complications and post-operative nausea. Only four out of 1,713 subjects treated with sugammadex experienced reoccurrence of blockade at the proposed licensed doses.

In the four phase III studies, the safety assessor was blinded to treatment allocation. In these studies, the adverse event profile of rocuronium plus sugammadex and vecuronium plus sugammadex was similar to all other comparators. In paediatric patients, sugammadex was well tolerated, however the number of patients was small.

A number of safety issues were identified as requiring continued pharmacovigilance or post-authorisation commitment. A total of seven subjects 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. However, continued pharmacovigilance is required for detection of such rare adverse events as hypersensitivity reactions.

Significant prolongation of the QTc interval was noted in all phase I to III studies, with the use of sevoflurane increasing the incidence of abnormally long QTc intervals. However, no *torsades des pointes* arrhythmia was noted in any of the study patients. The QTc prolongation is a concern in clinical situations when many other drugs affecting QT-interval are used concomitantly. Detailed evaluation of QTc prolongation is a post-authorisation commitment.

Summary of clinical effectiveness issues

In the above clinical studies, sugammadex when administered after rocuronium or vecuronium has been shown to provide more rapid reversal of neuromuscular blockade than neostigmine and when administered with rocuronium in the rapid sequence induction setting gave a faster mean recovery time than suxamethonium.

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. It is not effective with cisatracurium or atracurium which are also commonly used in practice in Scotland. How the introduction of sugammadex might influence the choice of neuromuscular blocking agent used routinely is not known. However, in rapid

sequence induction it would offer an alternative to suxamethonium in patients at increased risk of serious adverse events.

There has been considerable debate in the literature about the impact of sugammadex on clinical practice. Some authors believe that it is likely to significantly change practice although with some reservations about the still to be fully established safety profile. Others are more cautious and anticipate a more limited role for this drug, and reserve judgement until more data are available and question whether the reduction in time to reversal of blockade will translate into meaningful clinical advantage in elective surgery. This also is reflective of Scottish clinical opinion.

Patient numbers in the studies were small with a total safety database of 1,713 patients and therefore a larger population is needed to establish the risk of rare adverse events such as hypersensitivity reactions. The evidence base in patients with poorer physical status is also limited, as only one patient with ASA IV was included in the studies to date.

The effectiveness of sugammadex is dose dependent and this will have an impact on costs depending on the depth of neuromuscular block.

Summary of comparative health economic evidence

The manufacturer presented cost-effectiveness analyses of sugammadex for the reversal of neuromuscular blockade in two anaesthetic settings; elective surgery and rapid sequence induction (RSI).

In the elective surgery model, a decision tree model was used to compare sugammadex with neostigmine for the reversal of rocuronium and vecuronium induced shallow and profound block. Clinical data were taken from a systematic review of randomised controlled trials, including the pivotal clinical trials of sugammadex. Additional data used in the model relating to the incidence rates and consequences of prolonged paralysis were taken from a previously published meta analysis and observational studies. The manufacturer estimated that for the reversal of shallow block, sugammadex prevented 0.52 cases of prolonged paralysis at a cost of between £87.64 and £117.17, depending on the induction agent used. In the profound block scenario, the manufacturer estimated that sugammadex prevented 0.52 cases of prolonged paralysis at a cost of between £153.87 and £217.30. Compared with rocuronium plus neostigmine, rocuronium plus sugammadex was estimated to prevent 0.3 more cases of prolonged paralysis with estimated savings of £186.82 in the shallow block setting and £239.79 in the profound block setting.

There were a number of weaknesses with the analysis:

- The key to offsetting the increased cost of sugammadex was the inclusion of savings from reduced theatre time as sugammadex was shown to reduce the time taken for patients to recover from neuromuscular blockade. Experts have indicated that there are other factors that influence the time a patient spends in theatre, so reducing the time to recovery from neuromuscular blockade would not necessarily result in reduced theatre time. When these savings were removed, sugammadex became more expensive than all other comparators.
- Clinical experts have indicated that the monitoring of neuromuscular blockade may not always happen in practice. Therefore, even if time spent in theatre was partly influenced by the time to recovery from neuromuscular block it is not clear that monitoring would take place to allow these savings to be realised.
- The incidence rates of prolonged paralysis used in the model for the comparator treatments appear to be overestimates. This may overestimate the reduction in cases of

prolonged paralysis associated with sugammadex treatment. In addition, no cases of prolonged paralysis were reported in the pivotal trials for the sugammadex group and two cases were reported in one of the trials in the neostigmine group (resulting in an incidence of approximately 0.02). However, the values used in the model for neostigmine were taken from the literature, were based on neurophysiological rather than clinical assessment and were significantly higher than the rate observed in the trials. SMC clinical experts were asked to comment on the incidence rates of prolonged paralysis used in the model and they confirmed that the values were much higher than seen in practice.

- The outcome measure for the model was the number of cases of prolonged paralysis prevented. As Quality Adjusted Life Years (QALYs) have not been calculated it is difficult to judge whether the increased cost of sugammadex is justified by the increased effectiveness. This becomes an issue when the savings from reduced theatre time were removed.

Overall, there were significant weaknesses in the elective surgery model which undermine the economic case presented by the manufacturer. As a result, the manufacturer did not presented a sufficiently robust economic analysis for sugammadex to gain acceptance by SMC for use in this anaesthetic setting.

In the RSI model, suxamethonium was compared to rocuronium for induction followed by sugammadex if rapid reversal was required. Adverse events associated with each treatment were modelled and it was assumed that suxamethonium and sugammadex were equally effective in rapid reversal and this was supported by clinical trial data. The incidence rates of adverse events used in the model were based on a review of observational studies. Rapid reversal was estimated to be necessary in 0.025% of patients who required RSI. Therefore, only a small percentage of patients received sugammadex. The manufacturer estimated a cost per life year of £14,662 for rocuronium + sugammadex vs suxamethonium. This was based on an additional cost of £1.08 and a life year gain of 0.000075 and assumes both arms receive the same standard maintenance blocker and reversal agent if rapid reversal is not required.

There were some weaknesses with the analysis:

- The manufacturer stated that the main clinical advantage of using sugammadex in this scenario was avoiding adverse events associated with suxamethonium. While the difficulties in capturing the impact of rare adverse events within a QALY are acknowledged, as QALYs were not calculated it is difficult to understand the effect of avoiding these adverse events on patients.
- The sensitivity analysis showed that the results were most sensitive to changes in the incidence rate of anaphylaxis associated with suxamethonium. When the lower rate from the review of observational studies was used, the cost per life year increased to £45k.

Despite these concerns, SMC considered that the economic case for use of sugammadex in the RSI scenario when rapid reversal is required has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

For routine reversal of non-depolarising neuromuscular blocking agents, rocuronium and vecuronium, the comparators would be the anticholinesterases, neostigmine and edrophonium, possibly in combination with the antimuscarinics, atropine and glycopyrronium, to prevent some of the adverse effects of the anticholinesterases.

In rapid sequence induction situations the depolarising neuromuscular blocking agent, suxamethonium, would be the comparator.

Cost of relevant comparators

Routine reversal

Drug	Dose regimen	Cost per dose (£)
Sugammadex	**2 to 4mg/kg**	**60 to 119**
Edrophonium with atropine	500 to 700microgram/kg 0.6-1.2mg	27 to 34
Neostigmine	50 to 70 microgram/kg	1
Neostigmine with glycopyrronium	50microgram/kg 100microgram/kg	2

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4th November 2008. Costs are based on an adult weighing 70kg.

Immediate reversal

Drug	Dose regimen	Cost per dose (£)
Rocuronium plus sugammadex*	**1.2mg/kg 16mg/kg**	**364**
Suxamethonium	1mg/kg	2

* In the immediate reversal setting both rocuronium (£6 per dose) and sugammadex (£358 per dose) are given

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 November 2008. Costs are based on an adult weighing 70kg.

Additional information: budget impact

The manufacturer estimated savings of £50k in year 1 rising to £504k in year 5 when sugammadex is used in combination with rocuronium. When vecuronium is used as the induction agent, the manufacturer estimated savings of £20k in year 1 rising to £201k in year 5. These figures are based on an eligible patient population of 70,000 and market share estimates of 0.64% in year 1, rising to 6.5% in year 5. The budget impact estimates include savings from reduced theatre time.

When savings from reduced theatre time were removed, the manufacturer estimated the net drug cost to be £37,406 in year 1 rising to £381,076 in year 5. This was based on 448 procedures in year 1 rising to 4,564 procedures in year 5. The manufacturer confirmed that the budget impact estimates included both the elective surgery and RSI scenarios, with the RSI scenario accounting for approximately 8% of the total number of procedures eligible for sugammadex.

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.

This assessment is based on data submitted by the applicant company up to and including 09 December 2008.

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.

The undernoted references, shaded grey, were additional to those supplied with the submission.

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