נובמבר 2020

רופא/ה יקר/ה,
רוקח/ת יקר/ה,

הנדון: BRIDION® - ברידיון

Dosage form: Solution for Injection
Composition: Sugammadex 100 mg/ml

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל), מבקשת ליידע על עדכון העלון לרופא של התכשיר BRIDION.

להלן לשון ההתוויה המאושרת לתכשיר:
Reversal of neuromuscular blockade induced by rocuronium or vecuronium.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

עדכונים מהותיים שבוצעו בעלון לרופא:
טקסט שהוסף מודגש בקו תחתון, טקסט שנמחק מסומן בקו חוצה.

4.2 Posology and method of administration
…
Method of administration
Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, ~~directly into a vein or~~ into an existing intravenous line (see section 6.6). Sugammadex has only been administered as a single bolus injection in clinical trials.

4.4 Special warnings and precautions for use
…
Recurrence of neuromuscular blockade:
In clinical ~~trials~~ studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade, an incidence of 0.20% was observed for recurrence of neuromuscular blockade ~~was reported mainly when sub-optimal doses (in dose finding studies) were administered. In order~~ as based on neuromuscular monitoring or clinical evidence. The use of lower than recommended doses may lead to ~~prevent~~ an increased risk of recurrence of neuromuscular blockade~~, the recommended doses for routine or immediate~~ after initial reversal and is not recommended (see section 4.2 and section 4.8) ~~should be used~~.
…

Waiting times for re administration with neuromuscular blocking agents after reversal with sugammadex:

Table 1: Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex):

Minimum waiting time	NMBA and dose to be administered
5 minutes	1.2 mg/kg rocuronium
4 hours	0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium

The onset of neuromuscular blockade may be prolonged up to approximately 4 minutes, and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes after re-administration of rocuronium 1.2 mg/kg ~~(or 0.6 mg/kg)~~ within 30 minutes after sugammadex administration.

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~~Patients on a controlled sodium diet~~ Sodium:

~~Each ml solution contains up to 9.7 mg sodium. A dose of 23 mg sodium is considered essentially 'sodium-free'. If more than 2.4 ml solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet.~~This medicinal product contains up to 9.7 mg sodium per mL, equivalent to 0.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult

4.6 Fertility, pregnancy and lactation

…

Breast-feeding

It is unknown whether sugammadex is excreted in human breast milk. Animal studies have shown excretion of sugammadex in breast milk. Oral absorption of cyclodextrins in general is low and no effect~~s~~ on the suckling child is anticipated following a single dose to the breast-feeding woman. ~~Sugammadex can be used during breast-feeding.~~ A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sugammadex therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.8 Undesirable effects

Summary of the safety profile

Bridion is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess.

The most commonly reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication (Common (≥ 1/100 to < 1/10)).

Table 2: Tabulated list of adverse reactions

The safety of sugammadex has been evaluated ~~based on an integrated~~in 3,519 unique subjects across a pooled phase I-III safety database~~ of approximately 1,700 patients and 120 volunteers~~. The following adverse reactions ~~have been~~were reported ~~for surgical patients in clinical~~in placebo controlled trials~~:~~ where subjects received anaesthesia and/or neuromuscular blocking agents (1,078 subject exposures to sugammadex versus 544 to placebo):

[Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000)]

System organ class	Frequencies	Adverse reactions (Preferred terms)
Immune system disorders	Uncommon	Drug hypersensitivity reactions (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough
Injury, poisoning and procedural complications	Common ~~Uncommon~~	Airway complication of anaesthesia Anaesthetic complication (see section 4.4) ~~Unwanted awareness during anaesthesia~~Procedural hypotension Procedural complication

Description of selected adverse reactions

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Airway complication of anaesthesia:

Airway complications of anaesthesia included bucking against the endotracheal tube, coughing, mild bucking, arousal reaction during surgery, coughing during the anaesthetic procedure or during surgery, or anaesthetic procedure-related spontaneous breath of patient.

…

Procedural complication:
Procedural complications included coughing, tachycardia, bradycardia, movement, and increase in heart rate.

~~Awareness:~~
~~In sugammadex treated subjects a few cases of awareness were reported. The relation to sugammadex is uncertain.~~

Recurrence of neuromuscular blockade:
In ~~the data-base of pooled phase I-III~~clinical studies with ~~a placebo group, the~~subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade (N=2,022), an incidence of 0.20% was observed for recurrence of neuromuscular blockade as ~~measured with~~based on neuromuscular monitoring ~~was 2 % after sugammadex and 0 % in the placebo group. Virtually all of these cases were from dose-finding studies in which a sub-optimal dose (less than 2 mg/kg) was administered~~ or clinical evidence (see section 4.4).

Information on healthy volunteers:
~~Hypersensitivity reactions, including anaphylaxis, have been observed with sugammadex. In a study in healthy conscious volunteers (placebo, n=150; 4 mg/kg, n=148; and 16 mg/kg, n=150), hypersensitivity reactions were reported commonly with sugammadex 16 mg/kg (n=7, 4.7%), and uncommonly with sugammadex 4 mg/kg (n=1, 0.7%), and none with placebo (n=0, 0%).~~
~~In this study, dose dependent trends were also observed for dysgeusia, nausea and flushing.~~
A randomised, double-blind study examined the incidence of drug hypersensitivity reactions in healthy volunteers given up to 3 doses of placebo (N=76), sugammadex 4 mg/kg (N=151) or sugammadex 16 mg/kg (N=148). Reports of suspected hypersensitivity were adjudicated by a blinded committee. The incidence of adjudicated hypersensitivity was 1.3%, 6.6% and 9.5% in the placebo, sugammadex 4 mg/kg and sugammadex 16 mg/kg groups, respectively. There were no reports of anaphylaxis after placebo or sugammadex 4 mg/kg. There was a single case of adjudicated anaphylaxis after the first dose of sugammadex 16 mg/kg (incidence 0.7%). There was no evidence of increased frequency or severity of hypersensitivity with repeat dosing of sugammadex.
In a previous study of similar design, there were three adjudicated cases of anaphylaxis, all after sugammadex 16 mg/kg (incidence 2.0%).
In the Pooled Phase 1 database, AEs considered common (≥ 1/100 to < 1/10) or very common (≥ 1/10) and more frequent among subjects treated with sugammadex than in the placebo group, include dysgeusia (10.1%), headache (6.7%), nausea (5.6%), urticaria (1.7%), pruritus (1.7%), dizziness (1.6%), vomiting (1.2%) and abdominal pain (1.0%).

5.2 Pharmacokinetic properties
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Elimination:
In adult anaesthetized patients with normal renal function the ~~effective~~ elimination half-life ($t_{1/2}$) of sugammadex is about 2 hours and the estimated plasma clearance is about ~~84~~88 mL/min. A mass balance study demonstrated that > 90% of the dose was excreted within 24 hours. 96% of the dose was excreted in urine, of which at least 95% could be attributed to unchanged sugammadex. Excretion via faeces or expired air was less than 0.02% of the dose. Administration of sugammadex to healthy volunteers resulted in increased renal elimination of rocuronium in complex.

Special populations:

Renal impairment and age:

In a pharmacokinetic study comparing patients with severe renal impairment to patients with normal renal function, sugammadex levels in plasma were similar during the first hour after dosing, and thereafter the levels decreased faster in the control group. Total exposure to sugammadex was prolonged, leading to 17 -fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post-dose in patients with severe renal insufficiency.
In a second study comparing subjects with moderate or severe renal impairment to subjects with normal renal function, sugammadex clearance progressively decreased and $t_{1/2}$ was progressively prolonged with declining renal function. Exposure was 2-fold and 5-fold higher in subjects with moderate and severe renal impairment, respectively. Sugammadex concentrations were no longer detectable beyond 7 days post-dose in subjects with severe renal insufficiency.

Table 8: ~~Predicted~~A summary of sugammadex pharmacokinetic parameters ~~of sugammadex~~stratified by age ~~group~~ and renal function ~~based on compartmental modeling are~~is presented below:

הנתונים בטבלה 8 עודכנו, כמפורט בעלון המעודכן.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity potential, and toxicity to reproduction, local tolerance or compatibility with blood. ~~Sugammadex is rapidly cleared from most organs; however some retention of compound occurs in bone and teeth in the rat. The most likely component involved in the reversible binding is hydroxy apatite, the inorganic matrix in these tissues. Preclinical studies in young adult and mature rats have shown that this retention does not adversely affect tooth colour or bone quality, structure, turnover and development. In juvenile rats whitish discoloration was observed in the incisors and disturbance of enamel formation was observed upon repeated dosing, however at exposure levels of 48-480 times the clinical exposure at 4 mg/kg.~~

Sugammadex is rapidly cleared in preclinical species, although residual sugammadex was observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth colour or bone quality, bone structure, or bone metabolism. Sugammadex has no effects on fracture repair and remodelling of bone.

בעלון לרופא היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו. העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, חברת MSD ישראל, בטלפון 09-9533333.

BRIDION מופץ ע"י חברת נובולוג בע"מ.

בברכה,

אורית בילין
רוקחת ממונה
MSD ישראל

Refrences:
Bridion SPC 11/2020