16 September 2021
EMA/CHMP/555625/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sugammadex Mylan

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/005403/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CPP	Critical process parameter
CQA	Critical Quality Attribute
DSC	Differential Scanning Calorimetry
EC	European Commission
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GMP	Good Manufacturing Practices
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma optical emission spectrometry
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk Minimization Measures
QTPP	Quality target product profile
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 30 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Sugammadex Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2019.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults.
- For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data with the reference medicinal product Bridion instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Bridion, 100mg/ml, solution for injection
- Marketing authorisation holder: Merck Sharp & Dohme B.V
- Date of authorisation: 25-07-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/466/001 and EU/1/08/466/002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Bridion, 100mg/ml, solution for injection
- Marketing authorisation holder: Merck Sharp & Dohme B.V
- Date of authorisation: 25-07-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/466/001 and EU/1/08/466/002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	30 April 2020
The procedure started on	21 May 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2021
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one manufacturing and testing site in India between 4 - 8 January 2021. The outcome of the inspection carried out was issued on	20 July 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	26 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 May 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	12 August 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sugammadex Mylan on	16 September 2021

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Sugammadex Mylan 100mg/ml solution for injection. The originator product is Bridion 100mg/ml solution for injection first approved in Europe on 25 July 2008 (MAA No: EU/1/08/466/001-002, Merck Sharp & Dohme B.V).

Sugammadex is a modified gamma cyclodextrin which is a Selective Relaxant Binding Agent. It forms a complex with the neuromuscular blocking agents rocuronium or vecuronium in plasma and thereby reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

The Applicant has applied for the same indications as the originator:

- Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults.
- For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing 100 mg/mL of sugammadex sodium as active substance.

Other ingredients are hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

The product is available in type I clear glass vial closed with grey chlorobutyl rubber stoppers with aluminium light blue flip-off seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is octasodium 3({[(1*S*,3*S*,5*S*,6*S*,8*S*,10*S*,11*S*,13S,15*S*,16S, 18*S*, 20*S*, 21*S*,23*S*,25*S*,26*S*,28*S*,30*S*,31*S*,33*S*,35*S*,36*S*,38*S*,40*S*, 41*R*, 42*R*,43*R*, 44*R*,45**R**, 46*R*,47*R*, 48*R*,49*R*,50*R*,51*R*,52*R*, 53*R*, 54*R*, 55*R*,56*R*)-10, 15,20,25,30, 35,40-heptakis({[(2 carboxylatoethyl) sulfanyl] methyl})-41,42,43,44,45,46,47,48,49, 50,51,52, 53,54, 55,56-hexadecahydroxy-2,4,7,9, 12,14, 17,19,22, 24, 27, 29,32,34,37, 39-hexa decaoxanona cyclo[36.2.2.23,6 .28,11, .213,16 .218,21.223,26.228,31 .233,36] hexapentacontan-5-yl]methyl} sulfanyl)propanoate corresponding to the molecular formula $C_{72}H_{104}O_{48}S_8$ Na_8. It has a relative molecular weight of 2178.01 and the following structure:

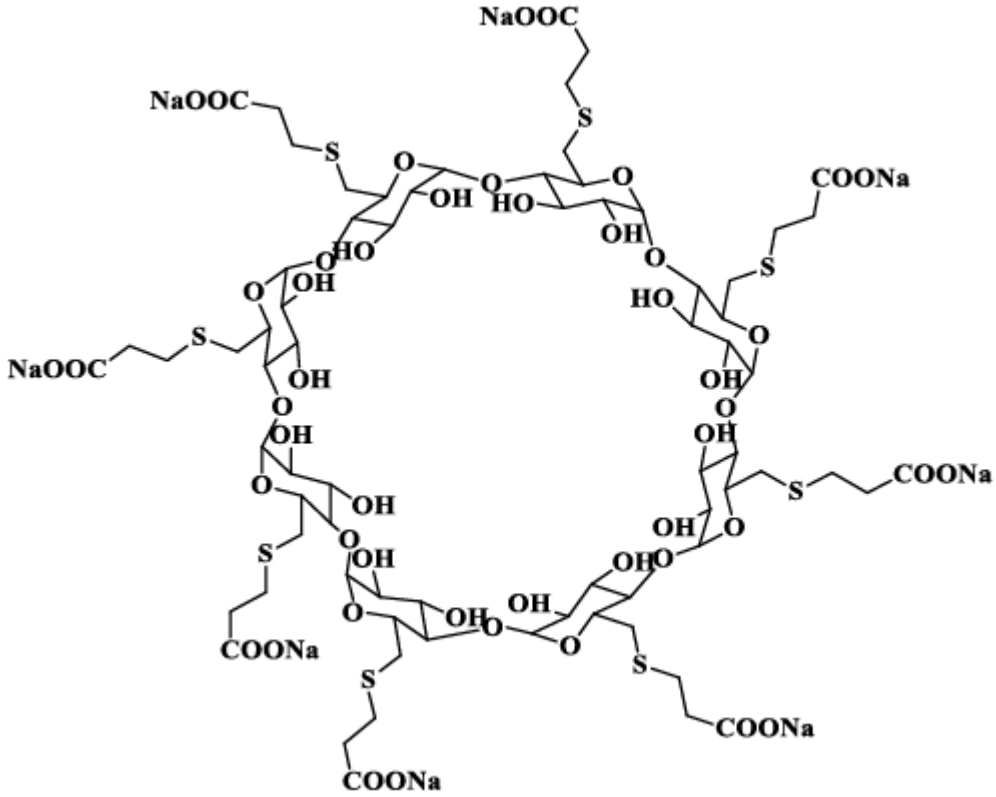

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated and the solid state properties confirmed by suitable analytical techniques.

The active substance is a highly hygroscopic white to off-white powder soluble in water and insoluble in methanol.

Sugammadex sodium is a modified γ-cyclodextrin, which contains 8 recurring glucose units each with 5 asymmetric carbon atoms, in total 40 asymmetric carbon atoms for the whole molecule. Chirality of the molecule is appropriately controlled, and is preserved throughout the manufacturing process of the active substance.

Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process of sugammadex sodium involves four stages using commercially available well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The dossier also included risk assessment on the potential presence of nitrosamines impurities in the active substance was provided.

The active substance is packaged triple laminated aluminium bag with oxygen absorber, which is lined with one black LDPE clear bag with oxygen absorber, layer of clear LDPE bag with silica gel and a layer of clear LDPE bag seal with nitrogen blanketing. The three LDPE bags are sealed with plastic liner seal. The material which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC), pH (Ph. Eur.), clarity (UV-Visible), absorbance (UV-Visible), water content (KF), sodium content (ICP-OES), assay (HPLC), related substances (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.), microbial test (Ph. Eur.), and foreign matter (visual).

The specification limits for the related substances are justified based on the ICHQ3A.

It has been adequately justified that no specific limits for elemental impurities are adopted in the active substance specification. It has been adequately justified the presence/absence of tests and limits for residual solvents.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data from three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, pH, clarity, water content, assay, related substances, microbial limit test, and bacterial endotoxin. The analytical methods used were the same as for release and were stability indicating.

Results from the accelerated and long-term stability studies revealed no significant changes in any of the parameters tested.

The active substance was also subjected to forced degradation (acid, base, oxidation, heat and light). The results showed that sugammadex sodium is more sensitive to acidic than the basic pH, thermal stress and is also very sensitive to oxygen.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period, in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as a clear and colourless to slightly yellow sterile, preservative-free solution free from visible particles. The finished product is available in 2 mL and 5 mL vials containing 200 mg and 500 mg of sugammadex, respectively.

The finished product has been developed as a generic medicinal product equivalent to the reference medicinal product, Bridion 100mg/mL solution for injection which is administered intravenously as a single bolus injection. The bolus injection may be given over 10 seconds, into an existing intravenous line. Therefore, given this, and the fact that the product contains the same active ingredient and inactive ingredients as reference medicinal product, in the same concentration, bioequivalence studies are not required for this product . Hence, the pharmaceutical equivalence of the product was established through the development studies, including stability studies.

Since the finished product is intended for intravenous administration, the applicant has adopted appropriate limits, in accordance with Ph. Eur., for microbial contamination and endotoxins in the active substance.

As indicated earlier, the proposed excipients are the same as those used in the reference product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A risk assessment of the overall finished product manufacturing process was performed to identify the high-risk steps that may affect the CQAs of the finished product. For each of these process steps, a risk assessment was subsequently conducted to identify potentially high-risk process variables which could impact the finished product CQAs. These variables were thoroughly investigated to better understand the manufacturing process and to develop a control strategy to reduce the batch failure. Component selection, equipment, and manufacturing were identified as main focus areas of evaluation during development. Considering the characteristics of the raw materials and the finished product, and based on the manufacturing process, critical control points (CCP's) and product specific requirements were identified to be monitored during manufacturing. Given that the product is to be sterile, autoclave suitability studies were carried out to determine whether Sugammadex Injection 100 mg/mL could be terminally sterilized.

During manufacturing process development, it was identified that several equipment components come in contact with the product during manufacturing and storage. There are chances of potential chemicals from these components leach into the finished product. To address this, a risk assessment to qualitatively describe the potential sources of extractables and leachables and justify the choice of equipment was conducted. There are multiple components that have the potential to leach unwanted contaminants into the finished product solution. In order to evaluate the acceptability for use of these various components extractables studies for each of these components were evaluated. The applicant is planning to conduct further extractable studies and a screening leachables study is also planned to further evaluate any potential risk to patient safety from unidentified or partially identified organic compounds.

The primary packaging is type I clear glass vial closed with grey chlorobutyl rubber stoppers with aluminium light blue flip-off seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. The manufacturing process consists of 6 main steps: dispensing, bulk compounding process, filtration, filling and sealing, terminal sterilization and visual inspection, following by labelling and secondary packaging. The process is considered to be a standard manufacturing process.

The finished product is terminally sterilized. The finished product is terminally sterilized using a reference condition of the Ph. Eur. 5.1.1 (⩾121 ° C, ⩾15 min in all units) and meets the bioburden requirements. The validation report is available at the finished product manufacturing site and available for inspection.

The vials are depyrogenated in a tunnel as a continuous process integrating the vial washing, followed by sterilization/depyrogenation to facilitate further filling & sealing process. The depyrogenation method uses a reference Ph. Eur condition.

The rubber stoppers are sterilized in an autoclave by steam sterilization process. The sterilization method uses a reference Ph, Eur. condition of the Ph. Eur.

The process validation will be performed on first three commercial batch size according to the process validation scheme provided. This is acceptable.

The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, specific optical rotation), pH (Ph. Eur.), light transmission at 650 nm (UV - Visible), color of solution (Ph. Eur.), osmolality (Ph. Eur.), particulate contamination-subvisible particles (light obscuration), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), extractable volume (Ph. Eur.), related substances (HPLC), assay (HPLC), sodium content (ICP-OES), and particulate contamination (Ph. Eur.).

The related substances are determined by a stability indicating validated analytical method. Applicable data and rationale supporting the justification for the proposed levels of the impurities in the finished product are provided.

A risk assessment on elemental impurities was done based on the information available from the respective vendors of the formulation ingredients and materials that come into the contact with the

finished product during manufacturing and storage. In addition, three batches of finished product from each fill were analysed for the presence of elemental impurities. The level of elemental impurities observed are less than 30% of PDE, option 3 of ICHQ3D is met. No further controls are required for monitoring elemental impurities in the finished product specification.

A risk evaluation concerning the potential presence of nitrosamines impurities in the finished product has been performed considering all suspected and actual root causes, in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standards used for testing are the same as for the active substance and are acceptable.

Batch analysis results are provided for three pilot scale batches of the 2 mL vials and three pilot batches of the 5 mL vials confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

Stability of the product

Stability data from three pilot scale batches of the 2 mL vials and three pilot batches of the 5 mL vials of finished product stored inverted and upright for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: description, identification, pH, light transmission at 650 nm, colour of solution, particulate matter, osmolality, bacterial endotoxins test, sterility, related Substances, assay, sodium content, and foreign matter. The analytical procedures used are stability indicating.

Under long term conditions no significant changes have been observed. In addition some samples of the finished product were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products (ICH Q1B). The product was found to be stable when stored in the secondary pack and complied with the specification.

Based on available stability data, the proposed shelf-life of 2 years and the storage recommendation store below 30° C. Do not freeze. Keep the vial in the outer carton in order to protect from light as stated in the SmPC (section 6.3) are acceptable

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product has been developed as a generic of Bridion 100mg/mL solution for injection. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Although the original information presented on the potential genotoxic impurities and the nitrosamine risk assessment was deemed incomplete, and CHMP raised major objections, the applicant provided satisfactory responses and all these issues were considered solved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory.

2.2.6. Recommendations for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the Summary of product characteristics (SmPC) of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Sugammadex Mylan manufactured by Mylan Ireland Limited is considered unlikely to result in any significant increase in the combined sales volumes for all sugammadex containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. No questions have been raised during the assessment.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Sugammadex Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. The clinical aspects of the SmPC are in line with the SmPC of the reference product.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Sugammadex Mylan 100 mg/mL is a solution for injection. The reference product is Bridion 100 mg/mL solution for injection, Merck Sharp & Dohme B.V., a CP product EMEA/H/C/000885.

No bioequivalence study was submitted to support the application. According to Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. This is the case here. Furthermore, both products contain the same excipients. A bioequivalence study is not required.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Conclusions on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate. No bioequivalence study was submitted to support the application, this is in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence. No questions were raised during the assessment.

Sugammadex Mylan is considered essentially similar to Bridion, Merck Sharp & Dohme B.V.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Delayed onset time or insufficient neuromuscular blockade at re-treatment with steroidal neuromuscular blocking agent • Slow recovery from neuromuscular blockade (Drug effect decreased) • Recurrence of neuromuscular blockade • Use of sugammadex in patients with renal impairment; after re-treatment with a steroidal NMBA delayed onset of neuromuscular blockade may occur • Anaesthetic complication • Hypersensitivity, including anaphylaxis/anaphylactic shock • Bronchospasm in patients with a history of pulmonary complications • Bradycardia
Important potential risks	• Bleeding complications in patients with coagulopathy • Capturing interactions (hormonal contraceptives, drugs yet to be marketed and other unknown drugs), leading to reduced efficacy • Displacement interactions (fusidic acid, toremifene, drugs yet to be marketed and other unknown drugs), leading to reduced efficacy
Missing information	• Exposure in infants and neonates • Exposure during pregnancy • Exposure human milk • Exposure in patients with hepatic impairment including hepatic impairment accompanied by coagulopathy

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance (PV) activities are considered adequate to monitor the safety of the medicinal product.

Routine PV activities are also sufficient to monitor the effectiveness of the risk minimisation measures (RMMs).

There are no on-going or planned additional ~~pharmacovigilance~~ PV activities.

2.5.3. Risk minimisation measures

The safety information in the PI is aligned to the reference medicinal product.

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. No additional RMMs are deemed necessary.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the originator Bridion (EMEA/H/C/0885) and the design and layout to the "in-house" style Mylan leaflet for Ogivri (EMEA/H/C/4916). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Sugammadex 100mg/ml solution for injection. The reference product Bridion is indicated for the treatment of reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient. No bioequivalence study was submitted to support the application, this is in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Sugammadex Mylan is favourable in the following indications:

- Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults.
- For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.