30 March 2023
EMA/CHMP/177188/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sugammadex Adroiq

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/006046/0000

Note

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

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List of abbreviations

AP	Applicant's part (or Open Part) of ASMF
API	Active pharmaceutical ingredient
AR	Assessment report
ASM	Active substance manufacturer
ASMF	Active substance master file = drug master file
AUC	Area under the curve
CFU	Colony forming units
Cmax	Maximum plasma concentration
CoA	Certificate of analysis
CPDB	Carcinogenic potency database
CPP	Critical process parameter
CQA	Critical quality attribute
CrCL	Creatinine clearance
CV	Coefficient of variation
DMF	N,N dimethylformamide
DSC	Differential scanning calorimetry
ECHA	European Chemicals Agency
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration
GC	Gas chromatography
GLP	Good laboratory practice
GMP	Good manufacturing practice
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HSDB	Hazardous substance data bank
HSGC	Headspace gas chromatography
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectroscopy
IPC	In-process control
IR	Infrared
IU	International units
KF	Karl Fischer titration
LDPE	Low-density polyethylene
LOD	Limit of detection
LOQ	Limit of quantification
LoQ	List of questions
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MDD	Maximum daily dose

MS	Mass spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOAEL	No-observed-adverse-effect-level
NTP	National toxicology program
OECD	Organisation for Economic Co-operation and Development
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PTC	Post tetanic counts
PTH	Parathyroid hormone
QOS	Quality overall summary
QP	Qualified person
QSAR	Quantitative structure activity relationship
QTPP	Quality target product profile
RH	Relative humidity
RP	Restricted part (or closed part) of ASMF
RRT	Relative retention time
SmPC	Summary of product characteristics
SRBA	Selective relaxant binding agent
$t_{1/2}$	Half-life
T2	Second twitch in the TOF stimulation
TLC	Thin layer chromatography
TTC	Threshold of toxicological concern
UV	Ultraviolet
USP	United States Pharmacopoeia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Extrovis EU Ltd. submitted on 31 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Sugammadex Adroiq, 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 16 December 2021.

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 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, justification for not submitting bioequivalence study with the reference medicinal product Bridion and literature data 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 8 years in the EEA:

- Product name, strength, pharmaceutical form: Bridion 100 mg/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/1/08/466/001-002

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

- Product name, strength, pharmaceutical form: Bridion 100 mg/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/1/08/466/001-002

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 appointed by the CHMP was:

Rapporteur: Kristina Nadrah

The application was received by the EMA on	31 March 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	12 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 December 2022
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	30 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	28 February 2023

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	16 March 2023
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 Adroiq on	30 March 2023

2. Scientific discussion

2.1. Introduction

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 product Sugammadex Adroiq 100 mg/mL solution for injection was developed as a generic version of Bridion 100 mg/mL solution for injection of Merck Sharp & Dohme B.V., The Netherlands.

The reference medicinal product in the European Union is Bridion 100 mg/mL solution for injection (Merck Sharp & Dohme B.V., The Netherlands) and authorised since 25 July 2008.

Pharmacotherapeutic group: all other therapeutic products, antidotes

ATC code: V03AB35

Therapeutic 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 100 mg/ml of sugammadex as active substance. The product contains the sodium salt (8 sodium ions per molecule of sugammadex).

Other ingredients are hydrochloric acid and/or sodium hydroxide (to adjust the pH) and water for injections.

The product is available in type I glass vials closed with chlorobutyl rubber stopper with red grain aluminium crimp-cap and flip-off cap as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of sugammadex sodium is 6A ,6B ,6C ,6D ,6E ,6F ,6G ,6H -octakis-S-(2-carboxyethyl)6A ,6B ,6C ,6D ,6E ,6F ,6G,6H -octathio-γ-cyclodextrin sodium salt (1:8) corresponding to the molecular formula $C_{72}H_{104}Na_8O_{48}S_8$. It has a relative molecular mass of 2177.97 g/mol and the following structure:

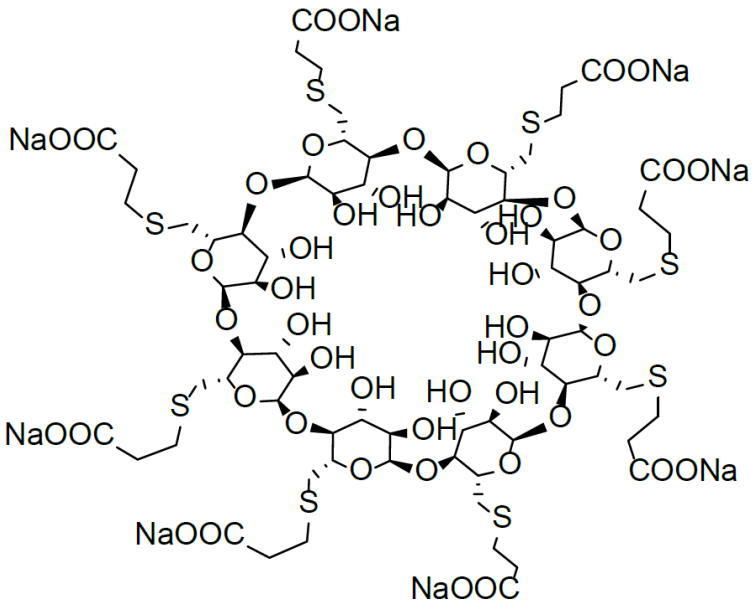

Figure 1: Active substance structure

The chemical structure of sugammadex sodium was elucidated by a combination of elemental analysis, ultraviolet spectroscopy (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (1 H and 13 C NMR) and mass spectrometry. The solid-state properties of the active substance were not analysed in detail as these are not important because the active substance is fully dissolved during manufacture of the finished product.

The active substance is a hygroscopic white to off white powder and is freely soluble in water. Sugammadex sodium exhibits stereoisomerism due to the presence of 40 chiral centres. The chirality is introduced with the starting material gamma cyclodextrin, a cyclic octamer of glucose. Enantiomeric purity is routinely confirmed by specific optical rotation of the starting material. Polymorphism has been observed for sugammadex sodium but is not important as the active substance is dissolved in the final formulation.

2.2.2.2. Manufacture, characterisation and process controls.

The active substance is manufactured by one manufacturing site.

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 ASMF holder is the single supplier of the active substance. Sugammadex sodium is synthesised in 3 main steps using 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 is in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities are well discussed with regards to their origin and characterised. Potentially genotoxic impurities have been discussed and evaluated. One genotoxic impurity is adequately controlled to acceptable levels based on ICH M7 control option 4.

The active substance is packaged in transparent LDPE bags (previously flushed with nitrogen) which are tied with plastic/nylon fastener. The bags are then first placed in a second transparent LDPE bag (previously flushed with nitrogen) containing a silica gel pack and tied with plastic/nylon fastener and then in a black LDPE bag (previously flushed with nitrogen) containing a silica pouch and sealed thermally. Then the pack is placed in a triple laminated bag (previously flushed with nitrogen) with silica gel pack, filled with nitrogen and sealed and this pack is inserted into a HDPE container and closed with plastic lids. The primary packaging material complies with the EC directive 2002/72/EC.

2.2.2.3. Specification

The active substance specification includes tests for description, solubility, appearance of solution (Ph. Eur.), identity (IR, HPLC), water content (KF), pH of solution 10% w/v, related substances (HPLC), content of one impurity (HPLC), assay (HPLC), sodium content (ICP-OES), residual solvents (GC, HPLC), microbial enumeration (Ph. Eur.), Nickel content (ICP-MS), bacterial endotoxins (Ph. Eur.) and specified microorganisms (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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 assay and impurities testing has been presented.

Batch analysis data from 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from 3 process validation batches of active substance from the proposed manufacturer stored in the intended commercial packaging for up to 12 months under long term conditions (25 ºC / 60% RH) and up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines are provided.

Photostability testing following the ICH guideline Q1B was performed on one batch as part of forced degradation studies. Further forced degradation studies were carried out in both solid and solution phase (light, heat, humidity, acid, base, oxidant) demonstrating the stability-indicating nature of the analytical methods.

The following parameters were tested: description, identity, water content, related substances, content of impurity mono hydroxy, assay and microbiological quality. The analytical methods used were the same as for release and are stability indicating. All parameters remained within the proposed specification. No significant increase of impurities and/or decrease of assay has been observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months with the storage condition "do not store above 25°C" in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

Sugammadex Adroiq 100 mg/ml solution for injection is a clear and colourless to slightly yellow brown solution free of visible particles. The finished product is presented in either 2 ml or 5 ml type I glass vials. Each vial of 2 ml contains sugammadex sodium equivalent to 200 mg sugammadex. Each vial of 5 ml contains sugammadex sodium equivalent to 500 mg sugammadex. The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

The finished product has been developed to be a generic equivalent to the reference medicinal product Bridion 100 mg/ml solution for injection. Consequently, the objective was to prepare a solution for injection which is essentially similar to the reference medicinal product.

The quality target product profile (QTPP) for the finished product was defined based information from the reference product. Relevant properties of the reference product were identified from the Package Leaflet and characterisation of the reference product. Definition of the QTPP allowed identification of potential critical quality attributes. The CQAs potentially being impacted by formulation and process variables were investigated during development studies. Risk assessments were used to support formulation and manufacturing development.

The active substance is highly soluble in water. Therefore, physicochemical properties of the active substance are not considered important for the quality of the finished product.

The only excipients used are water for injections along with hydrochloric acid and sodium hydroxide for pH adjustment. 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.

The composition of the finished product is qualitatively and quantitatively equivalent to the reference product – as such, no bioequivalence study was needed, and the excipients can be considered to be compatible.

Compatibility studies of finished product with diluents have been performed. The compatibility studies support the instructions for use and handling described in the SmPC.

During formulation development, the effects of various critical process parameters (CPPs) including processing aids were investigated to understand the impact on Critical Quality Attributes (CQAs) and to achieve the Quality Target Product Profile (QTPP). As a result, a suitable control strategy has been designed.

The development of the manufacturing process has been described. The risk associated with all process parameters and their respective process was identified.

The choice of the manufacturing process and critical process parameters have been justified in sufficient detail.

The primary packaging is type I glass vials closed with chlorobutyl rubber stoppers with red grain aluminium crimp-cap and flip-off cap. 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.

2.2.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site with further sites involved for secondary packaging and QC testing.

The manufacturing process consists of four main steps: bulk solution preparation, sterile filtration, aseptic filling in sterilised vials and terminal sterilisation. Terminal sterilisation *via* autoclaving is performed using Ph. Eur. reference conditions. The process is considered to be a standard manufacturing process.

The manufacturing process is presented in sufficient detail. Compounding, filling, packaging and sterilisation have been identified as critical steps of the manufacturing process. Acceptable holding times for the bulk solution before filtration, for the bulk solution after filtration and for the filled vials before terminal sterilisation are defined and these are supported by holding-time studies.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The shelf life is calculated in accordance with the Note for guidance on start of shelf life of the finished dosage form (CPMP/QWP/072/96).

2.2.3.3. Product specifications

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identify (HPLC), pH (Ph. Eur.), clarity of solution (Ph. Eur.), colour of solution (Ph. Eur.), organic impurities (HPLC), assay of sugammadex (HPLC), osmolality (in-house), extractable volume (Ph. Eur.), sterility (Ph. Eur.), particulate matter (visible and sub-visible particles), (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and container closure integrity (USP).

Release and shelf-life specifications for both presentations are acceptable and include all relevant parameters in line with ICH Q6A. The specification limits are the same for both presentations except for the extractable volume and are adequate. Levels of specified impurities are above the qualification limit at shelf-life but are toxicologically qualified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with principles of the ICH Q3D Guideline for Elemental Impurities. All potential sources of elemental impurities have been considered. Batch analysis data on 3 batches using an ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine 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 there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, assay and impurities testing has been presented.

Batch analysis results are provided for 3 batches confirming 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.

2.2.3.4. Stability of the product

Stability data from 3 batches of finished product of both presentations stored for up to 18 months under long term conditions (25ºC / 60% RH) and intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identity, pH, clarity of solution, colour of solution, organic impurities, assay of sugammadex, osmolality, sterility, particulate matter (visible and sub-visible particles) and bacterial endotoxins. The analytical methods used were the same as for release. The stability-indicating nature of the methods has been demonstrated. No significant changes were observed. All results are within the proposed specification limits.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

For paediatric patients, the medicinal product can be diluted to a concentration of 10 mg/ml as stated in the SmPC. An in-use stability study after dilution to 10 mg/ml has been performed. Compatibility for the diluents stated in the SmPC has been demonstrated. The storage conditions and the diluents used are the same as for the reference medicinal product.

Based on available stability data, the proposed shelf-life of 2 years as stated in the SmPC (sections 6.3 and 6.4) is acceptable with the following restrictions for in-use and storage:

- Store below 30°C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- After first opening and dilution chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 25°C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

2.2.3.5. Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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 way.

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 and pharmacokinetics data. Pharmacodynamic, pharmacokinetic and toxicological properties of sugammadex sodium are well known. As sugammadex sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The submitted non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product Bridion.

Additionally, to justify the limits of sugammadex impurities, the applicant has submitted in Modul 3 section P.5.6 *Justification of specification*, Toxicological study of sugammadex impurities.

2.3.2. Toxicology

Toxicological study (RCC Study Number 11167)

Repeated dose intravenous toxicity study with Sugammadex (sugammadex sodium as Sugammadex) enriched with Impurities in Wistar Rat

The purpose of this study was to assess the cumulative toxicity of Sugammadex (sugammadex sodium as Sugammadex) enriched with Impurities when administered to rat via intravenous route at once weekly for 4 weeks. The reversibility of treatment-related changes was assessed after a treatment-free 14-day recovery period.

Based on the data obtained in the toxicological study, no impurity related changes were observed in clinical signs, body weights, body weight change, feed consumption, haematology, clinical biochemistry, urine parameters, organ weights, macroscopic and microscopic examination at the higher dose of each

impurity enriched in 100 mg sugammadex/kg body weight. No cumulative toxicity of sugammadex with each impurity was observed.

It can be concluded that the proposed specifications limits for the specified impurities in drug substance and drug product, which are above qualification threshold are considered as toxicological qualified. Please see also under Quality section.

2.3.3. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Sugammadex Adroiq manufactured by Extrovis EU Ltd. 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.

2.3.4. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was provided and is considered adequate.

The non-clinical sections of the SmPC are acceptable and identical to the reference product Bridion.

The justification for the omission of the ERA is acceptable.

2.3.5. Conclusion on the non-clinical aspects

The non-clinical information provided in this application is acceptable to support the use of Sugammadex Adroiq in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Sugammadex Adroiq 100 mg/ml solution for injection. The originator product is Bridion 100 mg/ml solution for injection first approved in Europe on 25 July 2008 (EU/1/08/466/001-002, Merck Sharp & Dohme B.V).

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

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 proposed product Sugammadex Adroiq 100 mg/mL solution for injection is an aqueous intravenous solution containing the same drug substance sugammadex (as sugammadex sodium) with identical composition, as the reference product Bridion 100 mg/mL solution for injection, by Merck Sharp & Dohme B.V., the Netherlands (EU/1/08/466/001-002) authorised in the community since 25 July 2008.

As this is an abridged application, the applicant has not performed any efficacy or safety clinical studies with their formulation of Sugammadex Adroiq 100 mg/mL solution for injection in support of this application. Sugammadex is well-known active substance with established efficacy and safety.

The revised clinical overview on the pharmacokinetics, pharmacodynamics, efficacy and safety of sugammadex was provided and is considered adequate.

The proposed SmPC is in line with the SmPC of the reference product Bridion, Merck Sharp & Dohme B.V.

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 Rev.1).

2.4.2. Clinical pharmacology

No bioequivalence study was submitted to support the application as the proposed medicinal product Sugammadex Adroiq 100 mg/ml solution for injection has the same pharmaceutical form (solution for injection), dosage and route of administration (as an aqueous intravenous solution), has the same qualitative and quantitative composition in the active substance and inactive excipients, and is intended for the same therapeutic indication as the currently authorised Bridion 100 mg/mL solution for Injection by Merck Sharp & Dohme B.V (EU/1/08/466/001-002, 25-07-2008) (Reference product).

This is in accordance with the Guideline on the investigation of bioequivalence, which states "*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 authorised reference medicinal product."* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The lack of a bioequivalence study is thus acceptable.

2.4.2.1. Pharmacokinetics

As explained above Sugammadex Adroiq 100 mg/ml solution for injection is considered essentially similar to the Reference product Bridion 100 mg/ml solution for injection, Merck Sharp & Dohme B.V.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

The application contains an adequate review of published literature data on clinical pharmacology, efficacy, and safety.

Bioequivalence study is not required as the conditions of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) can be considered fulfilled.

Sugammadex Adroiq 100 mg/ml solution for injection is considered essentially similar to Bridion 100 mg/ml solution for injection, Merck Sharp & Dohme B.V.

Approval is recommended from the clinical point of view for Sugammadex Adroiq 100 mg/ml solution for injection.

2.4.4. Conclusions on clinical aspects

Sugammadex Adroiq 100 mg/ml solution for injection is considered essentially similar with Bridion 100 mg/ml solution for injection, Merck Sharp & Dohme B.V.

2.5. Risk Management Plan

2.5.1. Safety concerns

None.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of sugammadex 100 mg/mL solution for injection. The reference product Bridion 100mg/ml solution for injection is indicated for the following therapeutic 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.

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 nor on 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.

Sugammadex Adroiq 100 mg/mL solution for injection contains the same active substance as the Reference product Bridion 100 gm/mL solution for injection. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), "*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*.". Due to the same pharmaceutical form (solution for injection), dosage and route of administration (as an aqueous intravenous solution), the same qualitative and quantitative composition in the active substance and inactive excipients as the currently authorised reference product Bridion a bioequivalence study is not deemed necessary.

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 Adroiq is favourable in the following indication:

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.