19 May 2022
EMA/CHMP/564405/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sugammadex Fresenius Kabi

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/005760/0000

Note

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

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List of abbreviations

µCT	Micro computed tomography
AP	Applicant's Part of an ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
CEP	Certificate of Suitability of the Ph.Eur.
CL	Clearance
C_{max}	Maximum plasma concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DCP	Decentralised Procedure
DD	Delivered Dose
DPI	Dry Powder Inhaler
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
IPC	In-process control test
IR	Infrared
IV	Intravenous
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MRHD	Maximum recommended human dose
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMB	Neuromuscular blockage
NMBA	Neuromuscular blocking agents
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PP	Polypropylene
ppb	parts per billion
PTC	Post tetanic counts
PTH	Parathyroid hormone

QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
T2	Second twitch in the TOF stimulation
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TOF 0.9	Train-of-four ration of 0.9
TYMC	Total Combined Yeast/Mould Count
UV	Ultraviolet
V	Volume of distribution
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 2 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sugammadex Fresenius Kabi, 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 15 October 2020.

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) Directive 2001/83/EC.

The applicant applied for the following indication:

- Reversal of neuromuscular blockage induced by rocuronium or vecuronium in adults
- For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockage 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 and a bioequivalence study 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 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
- 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: 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 were:

Rapporteur: Agnes Gyurasics

The application was received by the EMA on	2 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 January 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	01 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of	19 April 2022

Outstanding Issues on	
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	04 May 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Fresenius Kabi on	19 May 2022

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.

Sugammadex 100 mg/mL solution for injection is 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 was first registered on 25 July 2008.

The therapeutic indications applied for are in line with the reference 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing 100 mg/ml of sugammadex. The product contains the sodium salt.

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

The product is available in type-I, glass vials closed with chlorobutyl grey rubber stoppers with aluminium flip-off over seal 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 6-perdeoxy-6-per(2-carboxyethyl)thio-γ-cyclodextrin sodium salt corresponding to the molecular formula $C_{72}H_{104}Na_8O_{48}S_8$. It has a molecular weight of 2178.0 g/mol and the following structure:

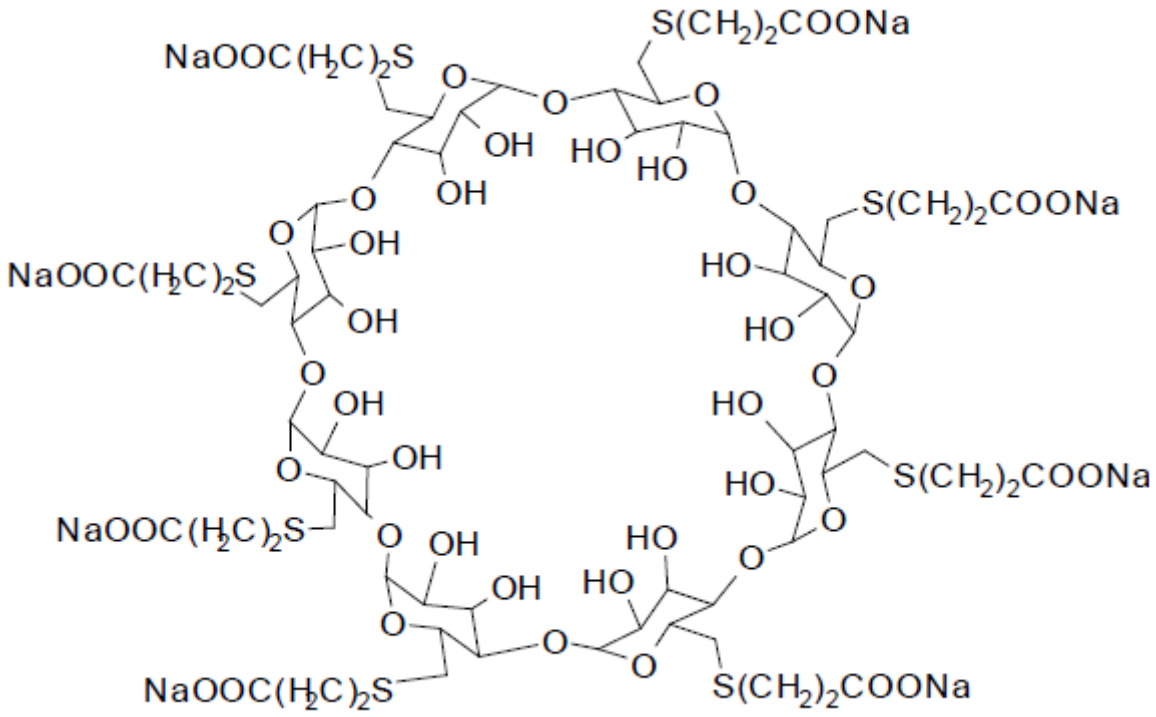

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of FT-IR, UV spectroscopy, mass spectrometry, NMR spectrometry, specific optical rotation and elemental analysis. The solid-state properties of the active substance were measured by XRPD.

The active substance is very hygroscopic, white to off-white powder, and freely soluble in water.

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 governed through its starting material (γ cyclodextrin) and it is preserved throughout the manufacturing process of the active substance.

Sugammadex shows polymorphism, however this property is not relevant as the finished product is an injectable dosage form with the active substance in solution.

2.2.2.2. 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 is comprised of two stages using commercially available well defined starting material with acceptable specification.

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 critical process parameters in the manufacturing process of active substance are identified and well controlled.

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 active substance is packaged in a low-density polyethylene (LDPE) bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended, with nitrogen and sealed with a tie rod. This bag is stored in another LDPE bag with nitrogen and sealed with a tie rod. This double bag is placed in triple-laminated aluminium pouch, with heat seal. The pouch is placed in a high-density polyethylene (HDPE) drum.

2.2.2.3. Specification(s)

The active substance specification includes tests for description/appearance (visual), identification (IR, HPLC, IC), pH (USP/in house), clarity of solution (Ph. Eur.), colour of solution (Ph. Eur.), water content (KF), specific optical rotation (USP/in house), sodium content (IC), related substances (HPLC), residual solvents (Ph. Eur.), assay (HPLC), bacterial endotoxins (Ph. Eur.) and microbiological quality (Ph. Eur).

Sugammadex is dosed based on body weight. In adults, the highest recommended dose is 16 mg/kg. Hence the maximum daily dose (MDD) for sugammadex is 1120 mg/day (based on an average body weight of 70 kg). Therefore, the ICH recommended thresholds for reporting, identification and qualification in the active substance are 0.05%, 0.09% (equivalent to 1 mg) and 0.09% (equivalent to 1 mg), respectively. The specification limits for the related substances are justified based on the ICHQ3A.

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 on 7 commercial 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 three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

The active substance has been subjected to photolytic stress conditions as part of the forced degradation studies performed with the HPLC assay and related substance methods. Based on the

observed results of the photolytic stress tests sugammadex was found to be stable (with no significant change).

Results on stress conditions (hydrolytic, acid, base, oxidative, thermal and photolytic degradation) were also provided on one batch. The highest degradation (~10%) was observed under oxidative stress.

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 no special storage conditions in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as solution for injection containing 100 mg/ml of sugammadex. The product contains the sodium salt. Three presentations of the finished product are proposed, i.e. 100 mg/1 ml, 200 mg/2 ml and 500 mg/5 ml. Each mL contains 100 mg sugammadex, which is equivalent to 108.8 mg sugammadex sodium. The aqueous solution is adjusted to a pH between 7 and 8 with hydrochloric acid and/or sodium hydroxide. The osmolality of the product is between 300 and 500 mOsmol/kg.

The finished product is a clear, colourless to slightly yellow solution filled into Ph. Eur. Type-I tubular clear glass vial stoppered with chlorobutyl grey rubber stopper and sealed with aluminium flip-off over seal.

The aim of the pharmaceutical development was to develop a generic formulation of Sugammadex 100 mg/mL solution for injection similar to reference medicinal product in Europe (EU), Bridion 100 mg/mL solution for injection of Merck Sharp & Dohme B.V., Netherlands, for intravenous use, that would be pharmaceutically and therapeutically equivalent to EU reference medicinal product.

Pharmaceutical development of the finished product contains QbD elements.

The critical quality attributes (CQAs) are identified based on QTPP, compendial requirements, reference medicinal product information and characterization, physicochemical properties of the active substance and developmental studies.

Risk assessment was used throughout development to identify potential attributes and process variables which can affect the critical product-specific Quality Attributes.

The active substance of the proposed finished product is sugammadex sodium, which is the same as that of reference medicinal product. Polymorphism and particle size of the active substance are not considered critical parameters as the active substance is dissolved in the finished 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.

The developed product is qualitatively and quantitatively identical to the reference product Bridion.

Compatibility studies have been performed with the finished product and manufacturing equipment and they demonstrate that they are compatible.

As per the reference product SmPC, Sugammadex should be administered intravenously as a single bolus injection into an existing intravenous line. In-line with reference product, compatibility of

mentioned intravenous infusion solutions (SmPC 6.6) with Fresenius Kabi's developed product was established. Parameters of appearance, clarity of solution and particulate matter were tested, and based on the results the developed finished product was found to be compatible with the listed infusion solutions.

Presence of ambient air in head space of vials leads to significant increase in several impurities on stability while no significant increase is observed in level of these impurities when not more than 5% oxygen is present in head space of vials. Both impurities are formed due to oxidative degradation and stability results depict the same trend. Therefore the headspace of the vials is flushed with nitrogen.

The finished product is terminally sterilised in the final container using moist heat sterilisation which has been appropriately validated.

No bioequivalence studies have been conducted in accordance with the "Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1,", as this product is to be administered by intravenous route and contains the same active substance, as the currently authorized reference medicinal product BRIDION 100 mg/mL solution for injection.

The primary packaging is type-I, glass vials closed with chlorobutyl grey rubber stoppers with aluminium flip-off over 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.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of six main steps: compounding, filtration, filling and sealing, terminal sterilisation, inspection and packaging. The process is considered to be a nonstandard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. The batch sizes are supported by process validation data, all validation parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. 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 terminal sterilization step is deemed as critical step of the manufacturing process of Sugammadex sodium solution for injection.

2.2.3.3. Product specifications

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), pH (Ph. Eur.), particulate contamination (Ph. Eur.), color of solution (Ph. Eur.), extractable volume (Ph. Eur.), clarity of solution (Ph. Eur), related substances (HPLC), bacterial endotoxins (Ph. Eur.), assay (HPLC), sterility (Ph. Eur.) and osmolality (Ph. Eur.).

The finished product specifications are considered acceptable. The proposed limits for specified impurities exceed the ICHQ3B qualification threshold. These higher limits are justified by the *qualified by use* principle with impurity levels found in the reference product. Potential genotoxic impurities are discussed, and the proposed control limits of these impurities are supported by toxicological assessments.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated 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 assay and impurities testing has been presented.

Batch analysis results are provided for eight commercial scale batches 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.

2.2.3.4. Stability of the product

Stability data from thirteen commercial scale batches of finished product stored for up to 24 months under long term conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: appearance, identification, pH, particulate contamination, color of solution, extractable volume, clarity of solution, related substances, bacterial endotoxins, assay, sterility and osmolality. The analytical procedures used are stability indicating.

No significant changes have been observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products There were no significant differences between samples stored in primary packaging, secondary packaging (similar as proposed for commercialization) and secondary packaging [wrapped in aluminium foil (control unit)].

The finished product is also intended to be administered for pediatric patients after dilution using sodium chloride 9 mg/mL (0.9%) to a concentration of 10 mg/mL. Chemical and physical in-use stability has been presented below after dilution in sodium chloride 9 mg/mL (0.9%) to a concentration of 10 mg/mL.

The in-use shelf-life of 48 hours at 2 – 25°C in line with the in-use shelf-life of the reference product and based on the provided stability data of the diluted injection has been accepted. The in-use storage time and conditions after first opening and dilution of the product, as stated in SmPC section 6.3, are acceptable.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions

as stated in the SmPC (section 6.3 and 6.4) are acceptable. The product should not be frozen and the vial should be stored in the outer carton in order to protect from light.

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 have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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 the clinic.

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 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 studies were submitted. This was justified by the applicant as the introduction of Sugammadex Fresenius Kabi 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

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 sections of the SmPC are acceptable and in line with that of the reference product.

The justification for omission of the ERA is acceptable.

2.3.4. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

This is an application for solution for injection containing sugammadex.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

2.4.2. Clinical pharmacology

No bioequivalence study has been submitted to support this application since Sugammadex Fresenius Kabi is an aqueous intravenous solution containing the same drug substance, as the chosen reference medicinal product Bridion 100 mg/mL solution for Injection by Merck Sharp & Dohme B.V (EU/1/08/466/001-002, 25-07-2008).

The proposed medicinal product has the same quantitative composition in terms of the active substance and same pharmaceutical form as the Reference product. Furthermore, the excipients used in Test product are the same as in the Reference medicinal product.

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 similar composition and route of administration a bioequivalence study is not deemed necessary by the CHMPP. The lack of an in vivo study is therefore acceptable.

2.4.2.1. Pharmacokinetics

As explained above no Bioequivalence study was submitted. Sugammadex Fresenius Kabi is considered equivalent to the Reference product Bridion, 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

In line with the Guideline on the Investigation of Bioequivalence, no bioequivalence study has been submitted to support the application.

Sugammadex Fresenius Kabi is considered equivalent to the currently authorized Bridion 100 mg/mL solution for Injection by Merck Sharp & Dohme B.V (Reference product).

There are no objections to approval of Sugammadex Fresenius Kabi from clinical point of view.

The CHMP considered that the clinical overview is adequate.

Conclusions on clinical aspects

Sugammadex Fresenius Kabi is considered equivalent to Bridion, Merck Sharp & Dohme B.V.

The clinical information provided in this application is acceptable to support the use of Sugammadex Fresenius Kabi in the applied indications.

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 0.3 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 Foscarnet sodium 24mg/ml solution for infusion and to Bridion 100 mg/ml solution for injection. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

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

- Reversal of neuromuscular blockage SMPC induced by rocuronium or vecuronium in adults
- For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockage 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.

Sugammadex Fresenius Kabi 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 similar composition and route of administration a bioequivalence study is not deemed necessary.

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

Having considered the data submitted in the application and available on the chosen reference medicinal product, 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 Fresenius Kabi 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.