26 April 2023
EMA/228402/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sugammadex Piramal

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/006083/0000

Note

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

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Table of contents

List of abbreviations

AS	Active substance
ASMF	Active substance master file = Drug master file
BDL	Below the limit of detection
γ-CD	Gamma cyclodextrine
CEP	Certificate of Suitability of the Ph. Eur.
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical reference substance
DL	Detection Limit
DMF	Drug master file = Active substance master file, ASMF
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
FID	Flame ionisation detection
FP	Finished product
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IR	Infra-red spectroscopy
KF	Karl-Fischer titration
LoA	Letter of access
LOD	Loss on drying
LoD	Limit of detection
LoQ	Limit of quantitation
MAH	Marketing Authorisation holder
MDD	Maximum daily dose
MS	Mass spectroscopy
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PDA	Photo diode array
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride

QbD	Quality by design
QL	Quantitation limit
QOS	Quality overall summary
QTPP	Quality target product profile
RH	Relative humidity
RMS	Reference member state
RSD	Relative standard deviation
Rrt	Relative retention time
Rt	Retention time
Rt	Room temperature
SD	Standard deviation
SWFI	Sterile water for injections
TGA	Thermo-gravimetric analysis
TLC	Thin layer chromatography
UV	Ultra violet spectrometry
XRD	X-Ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Piramal Critical Care B.V. submitted on 27 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Sugammadex Piramal, 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 24 February 2022.

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 and appointed by the CHMP were:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	27 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 January 2023
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	3 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 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	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	3 April 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	12 April 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 Piramal on	26 April 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.

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

The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of neuromuscular blockade. The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.

The product Sugammadex Piramal 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

Sugammadex can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing 100 mg/ml of sugammadex (as sodium salt) as active substance.

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

The product is available in clear glass vial closed with grey chlorobutyl rubber stopper with flip top red grain finish aluminium seal for the 2 ml vial or green grain finish aluminium seal for the 5 ml vial, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical (IUPAC) 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 corresponding to the molecular formula $C_{72}H_{104}Na_8O_{48}S_8$. It has a relative molecular mass of 2178.01 and the following structure (Figure 1):

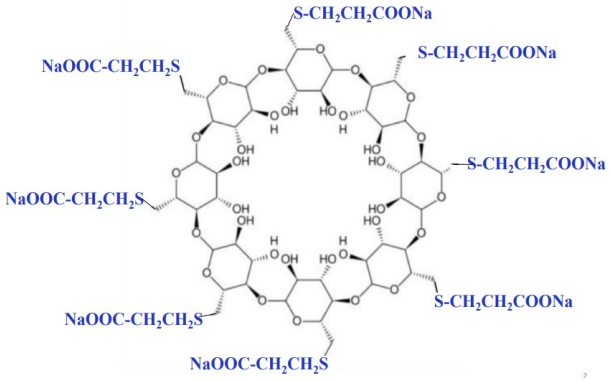

Figure 1. Active substance structure

The active substance (AS) was characterised by ^1H and ^{13}C NMR, MS, IR, UV and elemental analysis was performed on the sugammadex free acid. The obtained spectra are in agreement with the assigned structure.

Sugammadex sodium appears as white to off-white granules or powder. It is highly hygroscopic; it absorbs about 15% moisture from humid environment, however, the hygroscopicity is reversible. It is freely soluble in water, very slightly to slightly soluble in polar solvents and practically insoluble in acetonitrile, methanol and ethanol. Its solubility is not affected by pH in aqueous solutions.

The AS contains 8 recurring glucose units, each with 5 asymmetric carbon atoms, in total 40 asymmetric carbon atoms for the whole molecule. Chirality originates from γ-Cyclodextrin (specific rotation is + 174° to + 180°) and chirality is retained during the manufacturing process.

Sugammadex sodium shows polymorphism. It exists as composite mixture of different polymorphic forms including an amorphous form. However, as the drug product is a solution for injection, polymorphism is not considered to be of relevance.

2.2.2.1. Manufacture, characterisation and process controls

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 AS is synthesised in two chemical steps followed by purification using well-defined commercially available starting materials with acceptable specifications. The two proposed starting materials comply with the requirements of ICH Q11 and the corresponding Q&A document. Based on the known impurity profiles of both compounds and the established control strategy, this is considered sufficient to ensure that impurities generated in the manufacturing process of the starting materials do not impact the impurity profile of the final AS, consistently leading to active substance of appropriate quality.

Acceptable specifications and description of analytical methods are provided for all other reagents and solvents employed in the manufacturing process of the AS.

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

Potential and actual impurities were well discussed with regards to their origin and characterised. A specified impurity (process impurity) shows an alerting structure for mutagenicity. Therefore, in response to a Major Objection raised by CHMP the impurity has been classified in-line with ICH M7 and a suitable control strategy has been implemented taking also into account the proposed indication.

No significant changes with respect to the synthetic route have been taken place except for scale up related changes such as facility, equipment etc. These changes have been identified and the manufacturing process has been validated accordingly.

Sugammadex sodium is packaged in double transparent HDPE bags under nitrogen, placed inside a poly-laminated aluminium bag and stored inside a HDPE drum. The container closure system complies with EC 10/2011 as amended.

2.2.2.2. Specification(s)

The active substance specification includes tests for description (Ph. Eur.), identification (IR, HPLC), water content (KF), sodium content (Ph. Eur.), pH, (Ph. Eur.), clarity of water solution (visual), related substances (HPLC), monohydroxy Sugammadex sodium content (Ph. Eur.), assay (HPLC), residual solvents (GC and HPLC), total viable count (Ph. Eur.) and test for specified microorganisms (Ph. Eur.).

The specification for the AS by the finished product (FP) manufacturer is identical to the specification presented by the manufacturer in the ASMF.

All impurities (except from two specified ones) are controlled in line with ICH Q3A, taking into account the maximum daily dose (MDD) for sugammadex sodium (16 mg/kg/day), and hence the proposed limits are acceptable. The limits for those two specified impurities are justified by comparison with results obtained on the innovator Bridion, obtained on the EU market; this is acceptable. One specified impurity shows an alerting structure for mutagenicity and is hence controlled in-line with the requirements of ICH M7.

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 results for three batches of final drug substance by the drug product manufacturer were presented. The AS batches were used to manufacture the FP in the process validation studies. The results are within the specifications and consistent from batch to batch.

2.2.2.3. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions 30±2°C / 75±5% RH) and for up to six months under accelerated conditions (40±2°C / 75±5% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification (IR and HPLC), water content (KF), pH of 10% solution, related substances (HPLC), assay (HPLC) and microbial quality. The analytical methods used were the same as for release and were stability indicating. The active substance is very stable at accelerated and long-term conditions and no specific degradational trends are being observed. Only a

slight increase in water content is observable over time. Assay remains constant and the highest result obtained for total impurities is well within the specifications during long-term and accelerated testing.

Photostability was investigated during forced degradation studies. The AS did not show signs of degradation after exposure to light when protected by the primary packaging material.

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 36 months with the special storage condition "Store in airtight container, protected from moisture, light and air under dry and inert atmosphere, below 30 °C." is acceptable. Although the data demonstrates that a special temperature warning is not necessary, this was not raised as an issue as it does not affect patients compliance or safety.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

Sugammadex 100 mg/mL solution for injection is available in two different vial presentations, i.e. 2 mL and 5 mL. The different presentations of the are described as follows:

Strength	Description
200 mg / vial	Clear and colourless to slightly yellow brown solution free from visible particulates, in clear glass vials, stoppered with grey chlorobutyl rubber stoppers, and sealed with aluminium flip-off seals having PP discs (red).
500 mg / vial	Clear and colourless to slightly yellow brown solution free from visible particulates, in clear glass vials, stoppered with grey chlorobutyl rubber stoppers, and sealed with aluminium flip-off seals having PP discs (green).

Sugammadex 100 mg/mL solution for injection was developed as an equivalent generic to Bridion. The generic formulation is already defined by the composition of the reference product Bridion and consist of AS dissolved in water for injection and pH adjusted (using either HCl or NaOH). Therefore, no separate formulation experiments have been performed.

As sugammadex sodium is intended for preparation of parenteral medicinal product and is fully dissolved during the finished product manufacturing process, polymorphism and stability of the polymorphic form during storage are not considered relevant. Pharmaceutical development focused on CQAs and especially how these CQAs were impacted by changes in manufacturing process. Previous experience was used to determine the degree of risk associated with each process step and its effect on the CQAs of 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 presented in section 6.1 of the SmPC. and in paragraph 2.1.1 of this report.

The FP manufacturer applied quality by design (QbD) concepts to develop a generic medicinal product that is therapeutically / pharmaceutically equivalent to the reference medicinal product. The quality target product profile (QTPP) was defined based on characterisation of the reference product, the properties of the AS and the intended patient population. Risk assessment was used throughout development to identify potentially high-risk formulation and process variables, and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated during or after development to capture the reduced

level of risk based on knowledge gained through development. However, no design space is claimed.

Identification of critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the FP. Pharmaceutical development focused on those CQAs that could be impacted by a realistic change to the FP formulation or manufacturing process. The CQAs were selected based on prior information and knowledge gained from pharmaceutical development studies of the same or similar types of formulations.

According to the SmPC, the FP should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing intravenous line. The FP can be injected into the intravenous line of a running infusion with the following intravenous solutions:

- Sodium chloride 9 mg/mL (0.9 %)
- Glucose 50 mg/mL (5 %)
- Sodium chloride 4.5 mg/mL (0.45 %)
- Glucose 25 mg/mL (2.5 %)
- Ringers lactate solution
- Ringers solution
- Glucose 50 mg/mL (5 %) in sodium chloride 9 mg/mL (0.9 %)

Compatibility of the developed formulation with the different solutions was studied. No incompatibility was observed at the tested dilution ratios.

The primary packaging are colourless vials with a chlorobutyl rubber stopper, tightly closed and fixed with aluminium crimp cap. A coloured flip top is applied to differentiate the two vial presentations. The primary packaging 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 3 main steps: a simple preparation of a bulk solution, followed by sterile filtration and subsequent terminal sterilisation. Terminal sterilisation is achieved by a standard autoclave cycle . The process is thus considered to be a standard process.

A narrative description of the manufacturing process, the equipment, and the in process tests and limits for applied at each manufacturing step has been provided in the dossier. The established holding times of the bulk solution before and after filtration as well as the maximum acceptable overall process time are adequately justified.

The sterilisation process of the rubber stoppers and of the glass vials has been described and is acceptable.

Major steps of the manufacturing process have been validated by a number of studies. A summary of the process validation studies performed was provided. 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.

2.2.3.3. Product specification(s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV, HPLC), pH of solution (Ph. Eur.), colour and achromicity (visual), degree of colouration (Ph. Eur.), monohydroxy sugammadex (HPLC), assay (HPLC), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), uniformity of dosage units (Ph. Eur.), organic impurities

(HPLC), container closure integrity test (Ph. Eur.), sodium content (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and bacterial entotoxins (Ph. Eur.).

The ICH recommended impurities thresholds for reporting, identification and qualification in the FP are applied considering the maximum daily dose (MDD) for sugammadex is 1120 mg/day (based on an average body weight of 70 kg). Unspecified impurities are controlled in-line with ICH Q3B; this is acceptable. The proposed limits for certain specified impurities are above the ICH Q3B qualification threshold but these higher limits were justified by toxicological qualification. Based on this study, the proposed limits are considered acceptable.

The limit for combined assay, as well as total impurities at release and during shelf-life are based on process capabilities and results from the stability program and are deemed acceptable.

An elemental impurities (EIs) risk assessment was performed on the FP in-line with the parenteral route of administration. None of the elemental impurities was found above 30% of the respective PDE. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). 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 for control of the FP used have been adequately described and appropriately validated in accordance with the ICH guidelines. Forced degradation studies were performed in connection with the HPLC methods for assay and related substances. Peak purity was investigated and mass balance is demonstrated. Both methods are considered as stability indicating. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for three batches of each vial presentation are included. The tested batches correspond to the batches manufactured during process validation. All results comply well with the proposed specifications. The process is well controlled and FP with a consistent quality profile is obtained.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches for each vial presentation stored for up to 24 months under long term conditions (25±2°C / 60±5% RH) and for up to six months under accelerated conditions (40±2°C / 75±5% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, pH, colour of solution, osmolality, extractable volume, assay, related substances, sodium content, particulate contamination, sterility and BET. The analytical procedures used were the same as for release and are stability indicating.

Sugammadex 100 mg/mL solution for injection is very stable in the proposed container packaging system and only a slow increase of two specified impurities over time is noticeable. The highest value for total impurities after six months of accelerated testing was within the specifications. Similar levels for total impurities are obtained after 24 months long-term testing. Other parameters remain constant upon

storage under both testing conditions. The product remains sterile. No difference between FP stored in different orientations is observable.

A photostability study has been performed according to ICH Q1B on one batch of Sugammadex 100 mg/mL solution for injection in vials. The FP did show significant signs of degradation after exposure to light protected only by the primary packaging material. No degradation is observed for drug product protected by the secondary packaging system. The FP was hence considered to be photosensitive and the storage condition "*Keep the vial in the outer carton in order to protect from light*" is included in SmPC section 6.4.

The stability of the FP after applying multiple freezing – thawing cycles, was studied. No significant changes in physical nor chemical parameters were observed, demonstrating stability of the product with respect to freezing/thawing.

Compatibility with the intravenous solutions, as well as stability over 48 h at 2°C – 25°C was demonstrated as discussed above and the respective recommendations for use are stated in the SmPC (sections 6.4 and 6.6).

The proposed shelf-life of 24 months with the storage condition "Keep the vial in the outer carton in order to protect from light" is acceptable.

Based on available stability data, the proposed shelf-life of 24 months with the storage condition "Keep the vial in the outer carton in order to protect from light", stated in the SmPC (section 6.3 and 6.4) are acceptable.

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 MO raised during the procedure has been resolved by implementing of a suitable control strategy for the concerned impurity.

The FP is qualitatively and quantitatively identical to the reference product Bridion. The FP manufacturer applied quality by design (QbD) concepts to develop a generic medicinal product that is therapeutically / pharmaceutically equivalent to the reference medicinal product. However, no design-space is claimed.

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

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

None.

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 (ERA) studies were submitted. This was justified by the applicant as the introduction of Sugammadex Piramal manufactured by Piramal Critical Care B.V. 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 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.

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

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 Piramal 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 Piramal 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.

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. The proposed product Sugammadex Piramal 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. Considering this, the applicant has not performed any efficacy or safety clinical studies with their formulation of Sugammadex Piramal 100 mg/mL solution for injection in support of this application.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of sugammadex based on published literature. Sugammadex is well-known active substance with established efficacy and safety. The Sugammadex Piramal SmPC is in line with the SmPC of the reference product Bridion.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Sugammadex Piramal, 100 mg/mL is a solution for injection. The originator Bridion 100 mg/mL solution for injection from Merck Sharp & Dohme B.V. marketed in the Community is the reference medicinal product. 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 Rev.1/Corr **), 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.

As explained above, Sugammadex Piramal 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 clinical overview of published literature data on the clinical pharmacology, efficacy and safety. No post-marketing data are available. The medicinal product has not been marketed in any country.

Bioequivalence study was not submitted and 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 Piramal is considered essentially similar to Bridion, Merck Sharp & Dohme B.V.

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

2.4.4. Conclusions on clinical aspects

Sugammadex Piramal 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 solution for injection. The reference product Bridion is indicated for 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 application contains adequate non-clinical data. 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. The non-clinical overview was updated with a comparative discussion on the impurity profiles of the proposed product and the reference product.

The application contains adequate clinical data. 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 Rev. 1/Corr **); "*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. Sugammadex Piramal is considered essentially similar to Bridion, Merck Sharp & Dohme B.V.

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 Piramal 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.