10 November 2022
EMA/CHMP/906354/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sugammadex Amomed

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/005935/0000

Note

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

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List of abbreviations

AAS	Atomic absorption spectrometry
API	Active pharmaceutical ingredient
ASMF	Active substance master file
CHMP	Committee for Medicinal Products for Human use
DSC	Differential Scanning Calorimetry
EC	European Commission
EMA	European Medicines Agency
EPAR	European public assessment report
ERA	Environmental Risk Assessment
EU	European Union
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAH	Marketing Authorisation Holder
NMR	Nuclear magnetic resonance
PDE	Permitted daily exposure
PE	Polyethylene
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
RH	Relative humidity
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of product characteristics
TGA	Thermogravimetric analysis
UV	Ultraviolet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AOP Orphan Pharmaceuticals GmbH submitted on 8 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sugammadex Amomed, 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 20 May 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

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

The chosen reference product is:

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

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

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

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

- Marketing authorisation number: EU/1/08/466/001 and EU/1/08/466/002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Nevenka Trsinar Brodt

The application was received by the EMA on	8 November 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 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	22 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 September 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	10 October 2022

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	26 October 2022
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 Amomed on	10 November 2022

2. Scientific discussion

2.1. Introduction

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

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

The proposed product Sugammadex Amomed 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) authorized in the community since 25 July 2008.

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

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

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as 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 pH) and water for injections.

The product is available in type I clear glass vials closed with coated bromobutyl rubber stoppers sealed with an orange flip-off caps as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of sugammadex sodium is octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt corresponding to the molecular formula $C_{72}H_{104}Na_8O_{48}S_8$. It has a relative molecular mass of 2178 g/mol and the following structure:

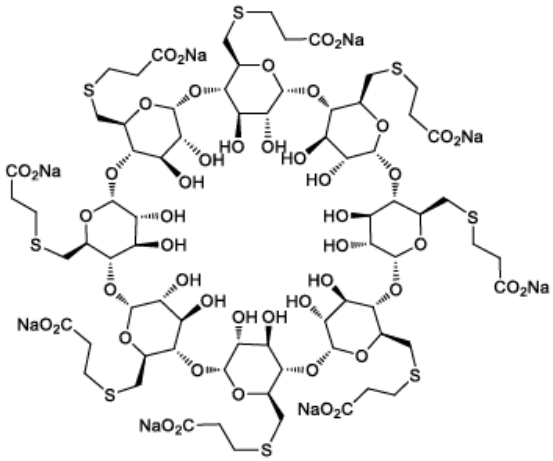

Figure 1: Active substance structure

The chemical structure of sugammadex sodium was elucidated by a combination of elemental analysis, ultraviolet spectroscopy (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR), high resolution mass spectrometry (HRMS) and x-ray single crystal diffraction. The solid-state properties were investigated by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), specific optical rotation and powder X-ray diffraction (XRD).

The active substance is a hygroscopic crystalline white or off-white powder and is freely soluble in water.

Sugammadex exhibits stereoisomerism due to the presence of 40 chiral centres. Enantiomeric purity is controlled routinely via the overall control strategy and confirmed by specific optical rotation of the active substance.

The polymorphic form was confirmed but is not important as the active substance is dissolved in the final formulation.

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. Sugammadex sodium is synthesized 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 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. Several genotoxic impurities are controlled in the active substance specification to acceptable levels.

The active substance is packaged in double low-density polyethylene (LDPE) bags, within laminated polyethylene terephthalate/aluminium/polyethylene (PET/Al/PE) pouches, stored within fibre drums. Relevant materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, specific optical rotation (polarimetry), identity (IR, HPLC), pH (Ph. Eur.), colour and clarity of solution (Ph. Eur.), related substances (HPLC and GC-MS), residual solvents (GC), water content (KF), sodium content (AAS), microbial limits (Ph. Eur.), bacterial endotoxins (Ph. Eur.), assay (HPLC) and impurities (GC-MS, HPLC).

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. Genotoxic impurities are controlled in line with 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 data from 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 production 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°C / 65% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on 1 batch. Forced degradation studies were also carried out in both solid and solution phase (light, heat, humidity, acid, base, oxidant) demonstrating the stability-indicating nature of the analytical methods.

The parameters tested are the same as for release with the exception of identity, sodium content and residual solvents which were omitted. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions. The active substance is particularly susceptible to oxidation when unprotected.

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 24 months when stored protected from light, not exceeding 30°C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Sugammadex Amomed 100 mg/ml solution for injection is a clear and slightly yellow solution. The pH is between 7 and 8 and osmolality is between 300 and 400 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 being essentially similar to the reference medicinal product. Relevant properties were identified

based on published information (EPAR and literature) and testing of batches of the reference product. Osmolality, pH and impurity levels of the reference product were targeted, and the applicant used an equivalent container closure system. The composition is qualitatively and quantitatively equivalent to the reference product – as such, no bioequivalence study was needed.

The active substance is highly soluble in water. As such, physicochemical properties are not considered important for the quality of the finished product. The active substance is sufficiently stable to allow terminal sterilisation.

The only excipients used are water for injections along with HCl and NaOH 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 and in paragraph 2.2.1 of this report.

The manufacturing process includes preparation of the bulk solution, filtration, filling into vials and terminal sterilisation. A feasibility study was performed to evaluate basic parameters for drug product manufacture. In the study, the impact of the filtration process and terminal sterilisation on assay and related substances has been evaluated. Drug product is sterilised by terminal sterilisation via autoclaving using Ph. Eur. reference conditions. The choice of the manufacturing process and critical process parameters, relevant for subsequent process validation, have been justified in sufficient detail.

The primary packaging is clear type 1 glass vials closed with coated bromobutyl rubber stoppers sealed with orange flip-off caps. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: compounding of API solution in water for injections, sterile filtration, aseptic filling in sterilised vials and terminal sterilisation. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive productions scale batches of finished product. Validation studies included filter validation, sterilisation and media fill steps. 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.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form including appearance (colour and clarity of solution, Ph. Eur.), identity (specific optical rotation, HPLC), pH (Ph. Eur.), osmolality (Ph. Eur.), relative density (Ph. Eur.), assay (HPLC, AAS), related substances (HPLC), extractable volume (Ph. Eur.), visible and sub-visible particles (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

Levels of impurities specified above the qualification limits have been justified.

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 3 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 was submitted but did not cover the active substance route initially. In response to a major objection, the risk assessment was revised to consider 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 production 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.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 18 months under long term conditions (25°C / 60% RH), up to 12 months under intermediate 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 are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, osmolality, absolute density, assay, related substances, extractable volume, visible and sub-visible particles, bacterial endotoxins and sterility. The analytical methods used were the same as for release. The stability-indicating nature of the methods has been demonstrated.

Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is photosensitive, but the secondary packaging provides sufficient protection.

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (sections 6.3 and 6.4) is acceptable with the following restrictions 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 2–25°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 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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. The major objection relating to the incomplete nitrosamines risk assessment was resolved by provision of further information.

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

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 clinical pharmacology, efficacy and safety is considered adequate.

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

The applicant has provided toxicological assessment of sugammadex impurities. Most of the impurities found in the synthesis of sugammadex are structurally related γ-cyclodextrins. It can be concluded that the impurities structurally related to alpha-cyclodextrin have a comparable pharmacological and toxicological profile to that of sugammadex. It is agreed with the applicant that no safety issues are expected. During the procedure, the applicant was requested to discuss the potential for skin sensibilization of one impurity. This is issue was sufficiently addressed.

2.3.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Sugammadex Amomed manufactured by AOP Orphan Pharmaceuticals GmbH 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 and not increased.

2.3.2. Discussion on non-clinical aspects

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

The safety of impurity SGT-R7 is sufficiently addressed.

The non-clinical sections of the SmPC are acceptable.

The justification for the omission of the ERA is acceptable.

2.3.3. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

During the procedure, the applicant was requested to review the clinical overview based on updated published literature. The revised clinical overview on the pharmacokinetics, pharmacodynamics, efficacy and safety of sugammadex was provided and is adequate. The Clinical sections of the SmPC of Sugammadex Amomed 100 mg/ml solution for injection is in accordance with the reference product Bridion ® 100 mg/ml for solution for injection, by Merck Sharp & Dohme B.V.,

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

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

2.4.1. Clinical pharmacology

2.4.1.1. Pharmacokinetics

No bioequivalence study was submitted to support the application as the proposed medicinal product Sugammadex Amomed 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 authorized 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.

2.4.1.2. Pharmacodynamics

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

2.4.2. Discussion on clinical aspects

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

No bioequivalence study has been submitted to support the application, which is in line with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

2.4.3. Conclusions on clinical aspects

Sugammadex Amomed 100 mg/mL solution for injection is considered essentially similar to Bridion 100 mg/mL solution for injection, Merck Sharp & Dohme B.V (Reference product).

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

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

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 Tetmodis. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Sugammadex Amomed 100 mg/mL solution for injection. The reference product Bridion 100mg/ml solution for injection 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 chemical-pharmaceutical documentation in relation to sugammadex sodium and finished product are of sufficient quality in view of the present European regulatory requirements.

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.

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

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 Amomed 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.