Amsterdam, 25 May 2023
EMA/CHMP/230066/2023
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Sugammadex Lorien

International non-proprietary name: sugammadex

Procedure No. EMEA/H/C/006115/0000

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
µg = mcg	Microgram
µM	Micromolar
AC	Adjudication committee
ACh	Acetylcholine
AE	Adverse event
ALP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AP	Applicant's part of an ASMF
API	Active pharmaceutical ingredient
AR	Assessment report
ASA	Anaesthesiologist
ASM	Active substance manufacturer
ASMF	Active substance master file
AUC	Area under the plasma concentration-time curve
B2MG	B2 microglobinuria
BIS	Bispectral index
BMI	Body mass index
CDs	Cyclodextrins
CEP	Certificate of suitability of the Ph.Eur.
CI	Confidence interval
CK	Creatinine phosphokinase
CL	Creatinine clearance
C_{max}	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMS	Concerned Member State
CoA	Certificate of analysis
CRS	Chemical reference substance (official standard)
CYP	Cytochrome P
DCP	Decentralised procedure
DD	Delivered dose
DPD	Dihydropyrimidine dehydrogenase

DPI	Dry powder inhaler
DSC	Differential scanning calorimetry
E	Edrophonium
EA	Emergence agitation
EC	Effective concentration
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good manufacturing practice
HDPE	High density polyethylene
HEK-29	Human embryonic renal cells
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonisation
IC50	The half maximal inhibitory concentration
IC90	The 90 % of the maximal inhibitory concentration
INR	International normalized ratio
IPC	In-process control test
IR	Infrared
IV	Intravenous
LC-MS/MS	Liquid chromatography-mass spectroscopy
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
MD	Mean difference
MS	Mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium Bromide
ND	Not detected

NLT	Not less than
NMB	Neuromuscular blockage
NMBA	Neuromuscular blocking agents
NMBD	Neuromuscular blocking drug
NMJ	Neuromuscular junction
NMR	Nuclear magnetic resonance
NMT	Not more than
NNT	Number needed to treat
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OR	Odds ratio
p	Probability
PACU	Post-anaesthesia care unit
PD	Pharmacodynamics
PDE	Permitted daily exposure
PE	Polyethylene
PK	Pharmacokinetics
Ph.Eur.	European Pharmacopoeia
PP	Polypropylene
ppb	parts per billion
PS	Physical status
PTC	Post tetanic counts
PTH	Parathyroid hormone
QOS	Quality overall summary
QTc	Corrected QT
R	Rocuronium
RBC	Red blood cell
RCT	Randomised controlled trials
RH	Relative humidity
RMS	Reference Member State
RP	Restricted part of an ASMF
RR	Risk ratio
RRT	Relative retention time

RSD	Relative standard deviation
RVA	Reversal agent
SD	Standard deviation
SmPC	Summary of product characteristics
SRBA	Selective relaxant binding agent
$t_{1/2}$	Half-life
T2	Second twitch in the TOF stimulation
TAMC	Total aerobic microbial count
TGA	Thermo-gravimetric analysis
TITCK	Turkish Medicines and Medicinal Devices Agency
tmax	Time taken to reach the maximum concentration
TOF 0.9	Train-of-four ratio of 0.9
TYMC	Total combined yeast/mould count
TSA	Trial sequential analysis
UK	United Kingdom
US / USA	United States of America
UV	Ultraviolet
V	Volume of distribution
XRD	X-ray diffraction

1. Recommendation

Based on the review of the data and the applicant's response to the CHMP list of questions (LoQ) on quality, safety, clinical, the generic application for Sugammadex Lorien with 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

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Outstanding Issues (see section 6).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

The choice of sterilisation method (aseptic filtration instead of terminal sterilisation) is not justified. Sugammadex containing drug products can be sterilised in the final container according to the scientific information found in the public domain.

According to the Guideline on the sterilisation of the medicinal product, drug substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) terminal sterilisation should not be ruled out purely on the basis of an increase in degradation products above the qualification thresholds in ICH Q3B (0.2% for the proposed drug product) or the impurity limits in ICH M7 for products in the scope of that guideline without additional justification. If impurities are either metabolites or are generated at levels already qualified, then terminal sterilisation is still considered feasible.

Deficiencies arising from concerns over the confidential (ASM - Active Substance Manufacturer restricted part) of the ASMF are mentioned in the appendix (this appendix is not supplied to the MAA). These concerns were conveyed in confidence to the holder of the ASMF.

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Inspection issues

1.2.1. GMP inspection(s)

The GMP certificate provided was considered acceptable in the context of this procedure.

The submitted QP declaration was acceptable.

1.2.2. GCP inspection(s)

Not applicable.

1.3. Similarity with authorised orphan medicinal products

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.

1.4. Derogation(s) from market exclusivity

Not applicable.

1.5. Information on paediatric requirements

Not applicable.

2. Executive summary

2.1. Problem statement

For a generic application, this section is not applicable.

2.2. About the product

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.

Pharmacotherapeutic group: all other therapeutic products, antidotes

ATC code: V03AB35

Therapeutic indications:

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

2.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not seek CHMP scientific advice pertinent to this product.

2.4. General comments on compliance with GMP, GLP, GCP

The GMP certificate provided was considered acceptable in the context of this procedure. The submitted QP declaration was acceptable.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(1) of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.

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

General comments on the submitted dossier:

In general, an adequate non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology has been submitted in the initial eCTD sequence of the application. However, the data presentation had several deficiencies. In CHMP day 120 List of questions the applicant was requested to address these as other concerns.

The revised non-clinical overview submitted in D121 response document was of acceptable quality.

In the initial eCTD sequence of the application the applicant provided a Clinical Overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of sugammadex based on

published literature and Bridion SmPC dated 2022. However, the data presentation had several deficiencies to be addressed.

The revised clinical overview submitted in D121 response document was of acceptable quality containing the outline of published literature and Bridion SmPC dated 2022 regarding the clinical pharmacology, efficacy and safety of sugammadex. Comparing the clinical overview to the SmPC there was still one missing information from the clinical overview for the applicant to amend.

2.5.2. Orphan designation

Not applicable.

2.5.3. Similarity with orphan medicinal products

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.

2.5.4. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.5. Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

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

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

The product is available in 5 ml, Ph. Eur. Type-I, tubular clear glass vials, stoppered with chlorobutyl grey rubber stopper and sealed with aluminium flip-off over seal.

Sugammadex 100 mg/ml solution for injection has two presentations: 200 mg/2ml and 500 mg/5 ml.

3.1.2. Active Substance

3.1.2.1. General information

Sugammadex 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.

Sugammadex is a modified Gamma-cyclodextrin.

The solution for injection contains 108.8 mg/ml of Sugammadex sodium (equivalent to 100 mg Sugammadex).

Sugammadex sodium is a known active substance; however, it is not official in a pharmacopoeia. The ASMF procedure is used, a letter of access is provided.

Sugammadex sodium is a white to off-white powder, freely soluble in water. It is very hygroscopic. Sugammadex sodium is a chiral molecule, however the isomerism of the active substance is not discussed, it is required. No information on polymorphism and particle size distribution of the drug substance is provided, however, these properties are not relevant, as the drug product is an injectable dosage form with the drug substance in solution.

3.1.2.2. Manufacture, process controls and characterisation

The information provided on the manufacturing process in the applicant's part of the ASMF is deemed acceptable. The two proposed starting materials are acceptable.

3.1.2.3. Specification (s)

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 drug substance are 0.05%, 0.09% (equivalent to 1 mg) and 0.09% (equivalent to 1 mg), respectively.

The proposed active substance specification includes tests for appearance, identification of active substance, pH, clarity and colour of solution, water content, sodium content, assay, related substances, residual solvents, bacterial endotoxin and microbial purity test. The proposed drug substance specifications are deemed acceptable. The DP manufacturer applies the same parameters and limits as the DS manufacturer to control the drug substance.

The analytical methods applied by the active substance manufacturers are described sufficiently, however some clarification is needed regarding microbiological purity test method. The in house analytical procedures used for the control of Sugammadex sodium have been validated, the methods are transferred from Manufacturer A to Manufacturer B, the methods have been adequately verified.

The in-house methods used by the drug product manufacturer for identification, assay, related substances, sodium content as well as the methods for determination of residual solvents were adequately validated and are suitable for the intended uses.

The information regarding API and impurity standards used by the active substance manufacturers are submitted. Sufficient characterisation data have been presented to confirm their structure. However information on currently used reference standards applied by manufacturer Amino is required. Some clarifications are also needed for reference standards used by drug product manufacturer.

The proposed packaging (double PE bags in laminated aluminium pouch with silica gel desiccant, placed into fiber or PE drums) is suitable for storage of Sugammadex sodium.

3.1.2.4. Stability

All stability results available following storage of the active substance at the long-term and accelerated conditions comply with the proposed specifications in section S.4.1. No significant change in the results

for any of the parameters tested is measured, only a slight increase (nevertheless well within the acceptance limits) of water content can be observed.

3.1.3. Finished Medicinal Product

3 . 1 . 3 . 1 . Description of the product and Pharmaceutical Development

Composition

The drug product is a 100 mg/ml solution for injection, containing the active substance Sugammadex sodium, dissolved in water for injection and adjusted to the required pH by hydrochloric acid and/or sodium hydroxide solution. Two presentations of the drug product are proposed, i.e. 200 mg/2 ml and 500 mg/5 ml. The drug 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 excipients and container closure systems are common for this type of dosage form.

Pharmaceutical development

The drug product Sugammadex 100 mg/mL solution for injection was developed as a generic equivalent to Bridion by Merck, Sharp & Dohme from the European market. The developed product is qualitatively and quantitatively identical to the reference product Bridion. The pharmaceutical equivalency of test product with the reference product Bridion, has been demonstrated with comparative study close to the shelf-life. Bioequivalence study does not need to be performed, since the product is to be administered as an aqueous parenteral solution containing the same active substance in the same concentration as the currently authorised product.

The manufacturing process development was carried out to obtain a stable product with similar characteristics compared to the reference drug product. The critical process conditions, namely oxygen sensitivity, thermal stability and photostability were investigated. Based on the results of this studies it has been concluded that the drug product is sensitive to oxidation, therefore nitrogen gas is used during the manufacture of the drug product; the steam sterilisation (terminal sterilisation) induced degradation in the drug product, therefore the applicant chose sterile filtration and aseptic filling instead of sterilisation in autoclave; the finished product is not photosensitive.

The choice of sterilisation method was not justified. According to the Guideline on the sterilisation of the medicinal product, drug substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) terminal sterilisation should not be ruled out purely on the basis of an increase in degradation products above the qualification thresholds in ICH Q3B (0.2% for the proposed drug product) or the impurity limits in ICH M7 for products in the scope of that guideline without additional justification. Major objection was identified. The applicant further justification has been submitted, nevertheless it cannot be considered as acceptable. Degradation products formed during sterilisation should be further investigated and terminal sterilisation should be used as for other authorised Sugammadex containing parenteral products.

The rubber stopper was tested by migration study. Some leachables exceed the concentration of the AET value, these leachables were evaluated according to ICH Q3B, however impurities extracted or leached from the container closure system are not within the scope of the above mentioned guideline. Leachables exceed of the AET value should be toxicologically qualified.

Compatibility of the drug product with one solution recommended in SmPC has been investigated, however question has been raised regarding compatibility of other solutions.

3.1.3.2. Manufacture of the product and process controls

The process involves preparation of bulk solution, sterile filtration, aseptic filling and packaging. The manufacturing process is considered as a non-standard process. The in-process controls presented are sufficient for this type of product. The manufacturing process has been described sufficiently in general, nevertheless some clarification is needed. The used sterilisation process is considered as not acceptable (see Pharmaceutical development).

The manufacturing process has been validated with three batches of 200 mg/2 ml presentations, along with three batches of 500 mg/5 ml presentation. Based on the submitted validation results all parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. Holding times are not fully justified, however, the issue is not pursued further as the whole sterilisation process is not acceptable.

3.1.3.3. Product specification (s)

The product specification includes tests for appearance, identification, clarity of solution, colour of solution, pH, extractable volume, uniformity of dosage units, osmolality, assay of Sugammadex, content of Monohydroxy derivative of Sugammadex, related substances, particulate contamination, bacterial endotoxins and sterility. In general the finished product specification is acceptable.

Analytical methods were adequately described. The in house methods were validated, however outstanding issues are still left concerning the validation of related substance method and stability indicating feature of the method.

Batch analysis data showing compliance with the proposed release specification were provided for the validation batches (3 batches of the 200 mg/2 ml presentations and 3 batches of the 500 mg/5 ml presentation). All parameters are within the specified limits. The submitted data demonstrate the consistency of the manufacturing process.

The discussion of impurities is still not sufficient. It is required that the origin/formation of degradation products taking into account the results of stress stability study, trends observed in stability studies and even literature data moreover the control strategy should be discussed in detail. For identified impurities characterisation data should also be presented.

Moreover the discussion of potentially genotoxic degradants is not sufficient, further evaluation is needed.

The submitted risk assessment on elemental impurities is acceptable. The drug product is no source for elemental impurities above the respective control threshold according to ICH Q3D.

Based on the performed risk assessment on nitrosamine impurities, no risk has been identified in Sugammadex 100 mg/ml solution for injection, the risk assessment is acceptable.

3.1.3.4. Stability of the product

The validation batches of Sugammadex 100 mg/mL solution for injection were included in the stability study.

The applicant submitted stability data up to 24 months long term (30°C ± 2°C, 75% RH ± 5% RH) and six months accelerated conditions (40°C ± 2°C, 75% RH ± 5% RH) for the drug product of each proposed

presentations. The data obtained after storage at long term and accelerated conditions show that the tested chemical, physical, and microbiological attributes of the finished product are within specification limits, however trend is observed for the level of Impurity A and B, their amounts increased. The other parameters show only variability.

Based on the photostabilty results the drug product is not sensitive to light.

The applicant proposes 24 months shelf-life. The proposed storage conditions for the drug product in the proposed container closure system are "Store below 30°C. Do not freeze."

In-use stability was investigated. The preparation of the diluted solution and storage conditions are in line with the paediatric use of the drug product described in SmPC. The test was carried out with samples close to the shelf-life too. No change was observed in any parameter during the tested period. In-use stability study should be performed also for other solutions mentioned in the SmPC.

3.1.3.5. Post approval change management protocol(s)

N.A.

3.1.3.6. Adventitious agents

None of the excipients in Sugammadex 100 mg/mL solution for injection are of human or animal origin.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the generic application for Sugammadex Lorien is not approvable since "major objection" has not been adequately answered, "major objection" is maintained, which preclude a recommendation for marketing authorisation at the present time.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the generic application for Sugammadex Lorien is not approvable since "major objection" has not been adequately answered, "major objection" is maintained, which preclude a recommendation for marketing authorisation at the present time.

3.1.6. Recommendation(s) for future quality development

Terminal sterilisation (in the final container by autoclave) should be applied instead of sterile filtration and aseptic filling.

3.2. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of sugammadex are well known. As sugammadex 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 was, thus, appropriate.

The non-clinical sections of the SmPC are acceptable and in line with that of the reference product.

It is considered that the updated non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

3.2.1. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted.

This was justified by the applicant as the introduction of Sugammadex Lorien 100 mg/ml solution for injection is considered unlikely to result in any significant increase in the combined sales volumes for all sugammadex sodium containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

A justification for the absence of a complete ERA is enclosed in Module 1.6.

3.2.2. Discussion on non-clinical aspects

A correctly updated non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The non-clinical sections of the SmPC were acceptable and in line with that of the reference product.

The justification for omission of the ERA is acceptable.

The non-clinical overview submitted initially on the pre-clinical pharmacology, pharmacokinetics and toxicology was, in general, adequate however some corrections of references to literature sources were needed. The revised non-clinical overview provided in the responses to D120 List of questions was then of acceptable quality, providing the appropriate information.

3.2.3. Conclusion on non-clinical aspects

There were no objections to an approval of Sugammadex Lorien from a non-clinical perspective.

3.3. Clinical aspects

This is a marketing authorisation application via the centralised procedure according to regulation (EC) No 726/2004 for Sugammadex Lorien 100 mg/ml solution for injection, submitted as a generic product of Bridion 100 mg/ml solution for injection centrally authorised medicinal product (first approved in Europe on 25 July 2008 (MAA No: EU/1/08/466/001-002, Merck Sharp & Dohme B.V)) according to Article 10(1) of Directive 2001/83/EC, with the same indication as the one of the 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.

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 Lorien 100 mg/mL solution for injection is an aqueous intravenous solution containing the same drug substance sugammadex (as sugammadex sodium) as the reference

product Bridion 100 mg/mL solution for injection, by Merck Sharp & Dohme B.V., the Netherlands (EU/1/08/466/001-002) authorised in the community since 25 July 2008.

As this is an abridged application, the applicant has not performed any efficacy or safety clinical studies with their formulation of Sugammadex Lorien 100 mg/mL solution for injection in support of this application.

In their response documentation to the CHMP day 120 List of questions the applicant provided a revised clinical overview now appropriately outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of sugammadex based on published literature and originator Bridion SmPC (dated 22 December 2022).

There was, however, still one piece of information missing from the clinical overview. The applicant was invited to update the overview with the following paragraph to support the SmPC adequately.

"A trial of 188 patients who were diagnosed as morbidly obese investigated the time to recovery from moderate or deep neuromuscular blockade induced by rocuronium or vecuronium. Patients received 2 mg/kg or 4 mg/kg sugammadex, as appropriate for level of block, dosed according to either actual body weight or ideal body weight in random, double-blinded fashion. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥ 0.9 in patients dosed by actual body weight (1.8 minutes) was statistically significantly faster ($p < 0.0001$) compared to patients dosed by ideal body weight (3.3 minutes)."

Sugammadex is well-known active substance with established efficacy and safety.

The overview justifies why there is no need to generate additional clinical data.

The clinical sections of the SmPC of Sugammadex Lorien 100 mg/ml solution for injection were in accordance with the reference product Bridion 100 mg/ml for solution for injection, by Merck Sharp & Dohme B.V., the Netherlands (EU/1/08/466/001-002) authorised since 25 July 2008 and updated on 22 December 2022.

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.

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

No bioequivalence study was submitted to support the application.

The proposed medicinal product has the same pharmaceutical form (solution for injection), dosage and route of administration (aqueous intravenous solution) intended for the same therapeutic indication, has the same qualitative and quantitative composition of the active substance and qualitatively the same excipients as the reference product Bridion.

Both products (test and reference products), contain 100 mg/ml sugammadex as sugammadex sodium and contain the excipients hydrochloric acid, sodium hydroxide used to adjust the pH of the solution. The proposed medicinal product is considered both therapeutically and pharmaceutically equivalent to the reference product Bridion.

This is in accordance with the Guideline on the investigation of bioequivalence, which states "*Bioequivalence studies are generally not required for a parenteral solution 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.

3.3.1.2. Pharmacokinetic conclusion

Sugammadex Lorien 100 mg/ml solution for injection is considered both therapeutically and pharmaceutically equivalent to the reference product Bridion 100 mg/ml solution for injection, Merck Sharp & Dohme B.V.

3.3.1.3. Pharmacodynamics

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

3.3.2. Discussion on clinical pharmacology

Not applicable.

3.3.3. Clinical efficacy

Sugammadex has been approved and used for more than 10 years for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population it is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

No new data on clinical efficacy have been provided and none were required for this application.

3.3.4. Clinical safety

Sugammadex has an established safety profile for more than 10 years in clinical use. It is generally well tolerated.

No own data on clinical safety have been provided and none are required for this application.

3.3.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.4. Discussion on clinical aspects

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

Sugammadex 100 mg/mL solution for injection (Test product) is considered essentially similar to the currently authorised Bridion 100 mg/mL solution for Injection by Merck Sharp & Dohme B.V (Reference product).

There are no major objections to approval of Sugammadex Lorien from the clinical point of view.

The clinical expert has provided an overview of the well-established clinical pharmacokinetics, pharmacology, efficacy and safety of sugammadex based on published literature references and originator Bridion SmPC (up to 2022).

CHMP considered that the revised clinical overview is not yet entirely adequate and can only be considered partly acceptable. The data presented had one minor deficiency that should be addressed by the applicant.

A new update of the clinical overview according to the request above (3.3. Clinical aspects) was necessary before approval.

It should be noted that the new information was not entered into the document using the track changes function, or highlighted in any other way, which made it difficult and time-consuming to discover the differences between the updated and the previous versions.

3.5. Conclusions on clinical aspects

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

CHMP considered that the updated clinical overview was not yet entirely adequate and can only be considered partly acceptable. The data presentation still had one minor deficiency that should be addressed.

The CHMP considers the following measure necessary to address the clinical issues:

Section 5.1 of the proposed SmPC includes a short description of a trial of morbidly obese patients. The applicant is requested to update the relevant section in the clinical overview to include discussion supported by suitable literature references, on the time to recovery from neuromuscular blockage induced by rocuronium or vecuronium in morbidly obese patients.

There were no objections to approval of Sugammadex Lorien from clinical point of view, provided that satisfactory response was given to the concern on the clinical overview as detailed above and in the List of Outstanding Issues.

3.6. Risk management plan

3.6.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.6.1.1. Discussion of the safety specification

No new risks have been identified for the generic product that are not recognised for the reference product and there are no outstanding issues.

3.6.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate, since it is in line with the safety specification of the originator's RMP (version number: 8.0).

3.6.2. Pharmacovigilance Plan

3.6.2.1. Routine pharmacovigilance activities

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance (PhV) is sufficient to identify and characterise the risks of the product.

3.6.2.2. Summary of additional PhV activities

On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
None				

3.6.2.3. Overall conclusions on the pharmacovigilance plan

The PRAC, having considered the data submitted, is of the opinion that routine PhV is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.6.3. Plans for post-authorisation efficacy studies

There are no planned or on-going post-authorisation efficacy studies imposed by the competent authority for Sugammadex 100 mg/mL solution for injection.

3.6.4. Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product. In line with the reference product the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.6.5. Summary of the risk management plan

The summary of the risk management plan is not considered acceptable. According to GVP Mod V rev 2 Guidance on the format of the risk management plan (RMP) in the EU – in integrated format, the Summary should be updated with following comments:

-Invented name should be used in the summary of the risk management plan as well as in the Product Overview Table.

-The following paragraph should be added to the first paragraph:

This Summary of the RMP for <invented name> should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of <invented name> 's RMP.

-The following paragraph should be included in the section 'I. The medicine and what it is used for';

Further information about the evaluation of <invented name>'s benefits can be found in <invented name>'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR Summary landing page>.

3.6.6. PRAC Outcome

N/A

3.6.7. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of outstanding issues.

3.7. Pharmacovigilance

3.7.1. Pharmacovigilance system

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

3.7.2. 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.

4. Benefit risk assessment

This application concerns a generic version of sugammadex sodium 100 mg/ml solution for injection. The reference product Bridion 100 mg/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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics, nor on the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature and originator's SmPC was considered sufficient.

Sugammadex Lorien 100 mg/mL solution for injection contains the same active substance as the reference product Bridion 100 mg/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.

However, a quality major objection on the sterilisation method of the drug product was still maintained.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities were required beyond those included in the product information.

The updated application provided with the responses to the CHMP day 120 List of questions contained adequate non-clinical and clinical data.

There was one aspect in the clinical overview that was inadequately demonstrated and was outlined in the List of Outstanding Issues:

Section 5.1 of the proposed SmPC includes a short description of a trial of morbidly obese patients. The applicant is requested to update the relevant section in the clinical overview to include discussion supported by suitable literature references, on the time to recovery from neuromuscular blockage induced by rocuronium or vecuronium in morbidly obese patients.

4.1. Conclusions

The overall benefit/risk balance of Sugammadex Lorien can not be concluded on at the moment, since a Quality major objection still pertains.