



Medicines & Healthcare products
Regulatory Agency



MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

**Suxamethonium Chloride 50mg/ml Solution for Injection
(suxamethonium chloride)**

UK Licence No: PL 00156/0110

Martindale Pharmaceuticals Limited



LAY SUMMARY

Suxamethonium Chloride 50mg/ml Solution for Injection (suxamethonium chloride)

This is a summary of the Public Assessment Report (PAR) for Suxamethonium Chloride 50mg/ml Solution for Injection (PL 00156/0110). It explains how the application for Suxamethonium Chloride 50mg/ml Solution for Injection was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Suxamethonium Chloride 50mg/ml Solution for Injection.

For practical information about using Suxamethonium Chloride 50mg/ml Solution for Injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Suxamethonium Chloride 50mg/ml Solution for Injection and what is it used for?

Suxamethonium Chloride 50mg/ml Solution for Injection is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Anectine Injection 5%.

Suxamethonium Chloride 50mg/ml Solution for Injection is used in anaesthesia to facilitate endotracheal intubation, mechanical ventilation and a wide range of surgical and obstetrics procedures. It is also used to reduce the intensity of muscular contractions associated with pharmacologically or electrically induced convulsions.

How does Suxamethonium Chloride 50mg/ml Solution for Injection for solution work?

This medicine contains the active ingredient suxamethonium chloride, which is a muscle relaxant. It works by helping the muscles to relax during surgery or medical procedures. It also reduces the strength of muscle contractions during fits or with electro-convulsion therapy (ECT).

How is Suxamethonium Chloride 50mg/ml Solution for Injection used?

This medicine can only be obtained with a prescription.

This medicine is usually given by bolus injection. In adults and children over 12 years, the dose is dependent on body weight, the degree of muscular relaxation required, the route of administration, and the response of individual patients.

To achieve endotracheal intubation Suxamethonium Chloride is usually administered intravenously in a dose of 1mg/kg. This dose will usually produce muscular relaxation in about 30 to 60 seconds and has a duration of action of about 2 to 6 minutes. Larger doses will produce more prolonged muscular relaxation, but doubling the dose does not necessarily double the duration of relaxation. Supplementary doses of Suxamethonium Chloride of 50% to 100% of the initial dose administered at 5 to 10-minute intervals will maintain muscle relaxation during short surgical procedures performed under general anaesthesia.

For prolonged surgical procedures, Suxamethonium Chloride may be given by intravenous infusion as a 0.1% to 0.2% solution, diluted in 5% glucose solution or sterile isotonic saline solution, at a rate of 2.5 to 4 mg per minute. The infusion rate should be adjusted according to the response of individual patients.

The total dose of Suxamethonium Chloride given by repeated intravenous injection or continuous infusion should not exceed 500 mg per hour.

In children from 1 to under 12 years, a dose of 1-2mg/kg is administered by intravenous injection.

Suxamethonium Chloride may be given intramuscularly to children at doses up to 4 mg per kg. A total dose of 150 mg should not be exceeded.

In infants under 1 year, a dose of 2mg/kg is administered by intravenous injection. Suxamethonium Chloride may be given intramuscularly to infants at doses of up to 4 to 5 mg per kg. A total dose of 150 mg should not be exceeded.

The dose in the elderly is the same as that described above for adults. The elderly may be more susceptible to cardiac arrhythmias, especially if digitalis-like drugs are also being taken.

What benefits of Suxamethonium Chloride 50mg/ml Solution for Injection have been shown in studies?

The company provided data from the published literature on suxamethonium chloride. No additional studies were needed as Suxamethonium Chloride 50mg/ml Solution for Injection is a generic medicine that is given as an injection and contains the same active substance, in the same concentration, as the reference medicine, Anectine Injection 5%.

What are the possible side effects of Suxamethonium Chloride 50mg/ml Solution for Injection?

As Suxamethonium Chloride 50mg/ml Solution for Injection is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine, Anectine Injection 5%.

For the full list of all side effects reported with Suxamethonium Chloride 50mg/ml Solution for Injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why was Suxamethonium Chloride 50mg/ml Solution for Injection approved?

It was concluded that, in accordance with EU requirements, Suxamethonium Chloride 50mg/ml Solution for Injection has been shown to have comparable quality and to be comparable to Anectine Injection 5%. Therefore, the MHRA decided that, as for Anectine Injection 5%, the benefits outweigh the identified risks and recommended that Suxamethonium Chloride 50mg/ml Solution for Injection can be approved for use.

What measures are being taken to ensure the safe and effective use of Suxamethonium Chloride 50mg/ml Solution for Injection?

A risk management plan (RMP) has been developed to ensure that Suxamethonium Chloride 50mg/ml Solution for Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Suxamethonium Chloride 50mg/ml Solution for Injection including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Suxamethonium Chloride 50mg/ml Solution for Injection

A Marketing Authorisation was granted in the UK on 09 October 2007.

The full PAR for Suxamethonium Chloride 50mg/ml Solution for Injection follows this summary. For more information about treatment with Suxamethonium Chloride 50mg/ml Solution for Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 5
III	Non-clinical aspects	Page 7
IV	Clinical aspects	Page 7
V	User consultation	Page 8
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 8
	Table of content of the PAR update	Page 11
	Annex 1	Page 12

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Martindale Pharmaceuticals Limited, a Marketing Authorisation for the medicinal product Suxamethonium Chloride 50mg/ml Solution for Injection (PL 00156/0110) on 09 October 2007.

This product is a prescription-only medicine (legal classification POM).

This was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, referring to the original product Anectine Injection 5% (PL 00003/5203), which was originally authorised to The Wellcome Foundation Limited in August 1985.

The product contains the active ingredient suxamethonium chloride, a depolarising neuromuscular blocker.

Suxamethonium Chloride 50mg/ml Solution for Injection is indicated for the following:

- To be used in anaesthesia as a muscle relaxant to facilitate endotracheal intubation, mechanical ventilation and a wide range of surgical and obstetrics procedures.
- It is also to be used to reduce the intensity of muscular contractions associated with pharmacologically or electrically – induced convulsions.

II QUALITY ASPECTS

II.1 Introduction

Suxamethonium Chloride 50mg/ml Solution for Injection is a clear, colourless solution. Each ml contains 50 mg of suxamethonium chloride.

Other ingredients consist of the pharmaceutical excipients, namely hydrochloric acid, water for injections and nitrogen.

The finished product is packaged in a Type I clear glass 2 ml ampoule.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

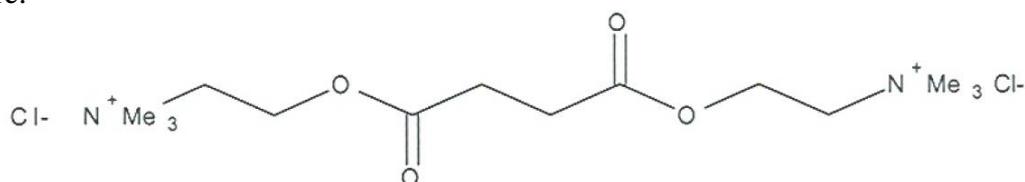
II.2 Drug substance

Suxamethonium Chloride

rINN: Suxamethonium chloride

CAS Number: 306-40-1

Structure:



Formula: $C_{14}H_{30}N_2O_4$

Chemical names: 2,2'-[(1,4-dioxobutane-1,4-diyl)bis(oxy)]bis(*N,N,N*-trimethylethanaminium)

MW: 290.40

Suxamethonium chloride is a white, crystalline powder. It is odourless, highly soluble in water, soluble in alcohol, slightly soluble in chloroform, and practically insoluble in ether.

The drug substance suxamethonium chloride is the subject of both British and European Pharmacopoeial monographs. The manufacture and specifications for active suxamethonium chloride are controlled by a certificate of suitability.

Suxamethonium chloride is packed in double-sealed clear polyethylene bags, which are placed in fibre drums.

II.3 Medicinal Product Pharmaceutical Development

The objective of the development programme was to formulate a stable product that could be considered a generic medicinal product of the currently licensed product, Anectine Injection 5% (PL 00003/5203).

A satisfactory account of the pharmaceutical development has been provided.

Comparable impurity and assay profiles have been provided for both the proposed product and the originator product.

All ingredients comply with their relevant European Pharmacopoeial monographs, with the exception of hydrochloric acid that is in compliance with a suitable in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

These products contain no excipients of animal or human origin and do not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided. A satisfactory batch formula has been provided for manufacture of the maximum batch size.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on small-scale batches of product and the results appear satisfactory. The applicant has committed to providing validation data for the first three production-scale batches produced.

Finished Product Specification

The proposed product complies with the general requirements of the Ph Eur for solutions for injection. The finished product specification provided is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set, with the storage conditions "Do not freeze", "Keep container in the outer carton" and "Store in refrigerator (2-8°C)". These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Suxamethonium Chloride 50mg/ml Solution for Injection.

II NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of suxamethonium chloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to suxamethonium chloride is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Suxamethonium Chloride 50mg/ml Solution for Injection.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of suxamethonium chloride. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

As the product is a simple aqueous solution for injection, with an essentially identical quantitative and qualitative composition to those for the reference product, no bioequivalence data were required. The applicant has demonstrated that Suxamethonium Chloride 50mg/ml Solution for Injection is a generic product of the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for

pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Suxamethonium Chloride 50mg/ml Solution for Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Important identified risks		
Safety concern	Summary of Routine Risk Minimisation Activities	Summary of Additional Risk Minimisation Activities
Bradycardia	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.4, 4.5 and 4.8 of the SmPC.	N/A
Overdose and muscle paralysis with Respiratory depression	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.3,4.4, 4.8 and 4.9 of the SmPC.	N/A
hyperkalaemia-related cardiac arrests	Routine risk minimisation measures are sufficient for this safety concern as information is included in Section 4.3,4.4,4.5, 4.8 of the SmPC.	N/A

Important potential risks		
Safety concern	Summary of Routine Risk Minimisation Activities	Summary of Additional Risk Minimisation Activities
Suxamethonium administration in patients with a personal or family history of malignant	Routine risk minimisation measures are sufficient for this safety concern as information is	N/A

hyperthermia	included in Section 4.3 of the SmPC.	
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Missing information		
Safety concern	Summary of Routine Risk Minimisation Activities	Summary of Additional Risk Minimisation Activities
Use in lactation	Routine risk minimisation measures are sufficient for this safety concern as information is included in Sections 4.6 of the SmPC.	N/A

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Suxamethonium Chloride 50mg/ml Solution for Injection.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's product and the reference product

are interchangeable. Extensive clinical experience with suxamethonium chloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling is presented below:

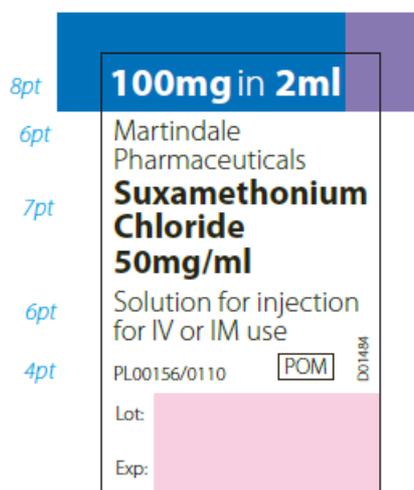




Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
To update the non-clinical and clinical overviews with new references. In addition, to update some aspects of the Quality related information, including the provision of a new QP declaration.	PL 00156/0110 - 0035	No	27/06/2018	03/08/2018	Approval	Y (Annex I)

Annex 1

Reference: PL 00156/0110 - 0035
Product: Suxamethonium Chloride 50mg/ml Solution for Injection
Marketing Authorisation Holder: Martindale Pharmaceuticals Limited
Active Ingredient(s): Suxamethonium chloride

Reason:

To update the non-clinical and clinical overviews (m4 and m5) with new references. In addition, to update some aspects of the Quality related information, including the provision of a new QP declaration.

Supporting Evidence

An updated non-clinical and clinical overview have been provided, along with an updated QP declaration.

Evaluation

Non-clinical

The non-clinical overview included a review of three recent (2011-14) scientific papers relevant to the safety of suxamethonium chloride, in particular the induction of malignant hyperthermia and to cause QT prolongation.

Two studies used a porcine model for malignant hyperthermia and its possible use in identifying characteristics for potential human extrapolation of any findings. The study reports disagreed with each other in the role that succinylcholine has to play. Malignant hyperthermia is a potential risk in humans and is being monitored in the current risk management plan.

The third study highlighted the potential of suxamethonium chloride to cause QT prolongation. The applicant states that this has not been observed in humans and does not feature in the current label for suxamethonium chloride and has not been repeated in any case studies. The report states that the effects of anaesthetic drugs and techniques on electrocardiographic torsadogenic markers should be considered in the perioperative management of patients with pre-existing repolarization abnormalities.

Clinical

The MAH has submitted an updated clinical overview. The overview includes sections on clinical pharmacology, efficacy and safety, and is supported by 48 references.

Suxamethonium has a well-established efficacy and safety profile in the EU. The submitted clinical overview adequately summarises the current knowledge relating to the clinical pharmacology, efficacy and safety of suxamethonium, in the approved indication. The overview is adequately supported by references, which are included in module 5.

The MAH has not identified any new safety concerns. Therefore, changes to the product information are not required.

Quality

Section 3.2.P.2 (Pharmaceutical Development) of the dossier has been updated to reflect some recent changes. The quality related dossier updates are considered to be acceptable. An acceptable QP declaration has been submitted.

Conclusion

Suxamethonium chloride is a well-established product which has been used in clinical practice since 1961. The compound is accepted and established in the proposed treatment. Further non-clinical studies are not warranted and there are no non-clinical objections to the grant of this variation for

suxamethonium chloride 50mg/ml solution for injection.

The updated clinical overview is acceptable. The benefit risk remains positive.

The quality related dossier updates are considered to be acceptable, including the provision of an updated QP declaration.

Decision

Approved on 03 August 2018.