IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Syrisal 1mmol/ml oral solution
Sodium chloride
PA22697/016/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5377/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0786/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/016/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy the Member States considered that the application for Syrisal 1 mmol/ml Oral Solution (PL 39307/0001; UK/H/5377/001/DC), is approvable. This product is a prescription only medicine (POM), indicated for the treatment and prophylaxis of sodium chloride deficiency.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and The Republic of Ireland as Concerned Member State (CMS). The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

The active ingredient, sodium chloride, is the principle salt involved in maintaining the osmotic tension of blood and tissues. Changes in osmotic tension influence the movement of fluids and diffusion of salts in cellular tissue.

Syrisal 1 mmol/ml oral solution provides a source of sodium (in the form of sodium chloride) where a deficiency exists.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use. Bioequivalence studies are not necessary to support this application.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 15 August 2016). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 39307/0001) for this product on 05 September 2016.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

This product is an aqueous solution for oral administration containing 1 mmol (58.44 mg) of sodium chloride per ml, as an active ingredient. The excipients present in this product are glycerol (E422), sodium citrate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and purified water.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The finished product is packaged in an amber or clear glass bottle with child resistant plastic screw cap containing 100 ml or 300 ml. The bottle is packed in a cardboard carton containing a 20 ml oral dosing syringe with 1 ml graduation mark and a syringe adaptor.

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

INN:	Sodium chloride
PhEur name:	Sodium chloride
Chemical name(s):	Sodium chloride
Molecular formula:	NaCl
Molecular weight:	58.44 g/mol
Appearance:	White or almost white, crystalline powder, colourless crystals or white or almost white pearls.
Solubility:	Freely soluble in water and practically insoluble in anhydrous ethanol.

Sodium chloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, sodium chloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious and stable oral solution containing 1 mmol/ml of sodium chloride.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. A validation report for commercial scale batches has been provided. The process validation data provided is satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that 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 and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with no special storage conditions has been set. Once the bottle is opened the product must be discarded after 30 days.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

As sodium chloride is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. An overview based on a literature review is appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment. This is acceptable as sodium chloride is an electrolyte and is exempt from the requirement to conduct an ERA.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

Sodium chloride is a well-established active substance and has been available for many decades worldwide including the EU. The details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

The clinical efficacy of sodium chloride is well-established. This was supported by the review of the bibliographic data. No formal dose ranging study data have been provided regarding the optimum dose of sodium chloride oral solution for the treatment of chronic sodium depletion. The treatment of sodium

chloride deficiency by the administration of sodium chloride is self-evident from a physiological viewpoint. This is supported in practice by the well established use and there is a general agreement regarding its benefits as described in the relevant clinical textbooks and other reference publications.

Overall the proposed Summary of Product Characteristics (SmPC) dosing regimen is acceptable in spite of lack of data to support the exact dosing schedule.

IV.5 Clinical safety

With regard to the safety aspects, the adverse events of sodium salts are attributable to electrolyte imbalances caused by excess sodium. General adverse effects of sodium chloride excess in the body focus mainly on gastrointestinal disorders as a result of excessive amounts of salt in the stomach, and the effect of systemic sodium levels on blood pressure.

Although the side effects of the current product are unknown, in general these are associated with high levels of sodium chloride in the body (hypernatraemia). Features of hypernatraemia are well known and are adequately included in the proposed SmPC.

No new safety data were submitted and none were required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profile of sodium chloride is well-known.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, 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 Syrisal 1 mmol/ml Oral Solution.

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypernatremia and conditions that increase the risk of	The risks of hypernatremia associated with the use of the drug	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
hypernatremia (post-operative use, impaired cardiac or renal function)	product and risks associated with the use of the drug product in patients with conditions that increase the risk of hypernatremia are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	
Hypertension	The risk of hypertension associated with the use of the drug product is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Situations in which salt retention is undesirable (such as oedema, heart disease, cardiac decompensation, and primary or secondary aldosteronism, or where therapy is being given to produce salt and water loss)	The risks associated with situations in which salt retention is undesirable (such as oedema, heart disease, cardiac decompensation, and primary or secondary aldosteronism, or where therapy is being given to produce salt and water loss) are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Hypersensitivity	The risk of hypersensitivity associated with the use of the drug product is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Overdose	The risks associated with the overdose of the drug product are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risks		
Dehydration	The risk of dehydration associated with the use of the drug product is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Conditions associated with sodium retention (such as hypertension, especially hypertensive patients with chronic renal failure, heart failure, peripheral and	The risks associated with the use of the drug product in conditions associated with sodium retention (such as pre-eclampsia) are described in the SPC, and appropriate advice is provided to the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
pulmonary oedema, renal impairment and pre-eclampsia)	prescriber to minimise these risks.	
Use in elderly	The risk associated with the use of the drug product in the elderly is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with pseudohyponatraemia	The risks associated with the use of the drug product in patients with pseudohyponatraemia are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Missing information		
Use in patients with cystic fibrosis	The information regarding the risks associated with the use of the drug product in patients with cystic fibrosis, particularly the risk of dehydration, is not available. A specific adverse event questionnaire for collection of data on dehydration in children with cystic fibrosis has been developed and will be used to collect this information.	Not applicable
Use in young patients	The information regarding the risks associated with the use of the drug product in young patients is not available, so prescriber is suggested to take extra care while administering the drug product to very young patients.	Not applicable
Safety of long-term use	An adverse event follow-up questionnaire for patients on long-term Syrisal therapy will be filled, and data will be collected. Information on the safety of long-term use of oral hypertonic sodium chloride will be collected. The risks associated with the long-term use of the drug product will be identified, characterised, prevented and minimised.	Not applicable
Safety in newborn (neonates), children and patients with impaired liver or kidney function	The information regarding dosage adjustment in paediatrics and patients with impaired liver or kidney function is described in the SPCand appropriate advice is provided to the prescriber.	Not applicable

IV.7 Discussion on the clinical aspects

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The publicly available bibliographic data does support the claim of well-established use for the sought indication in the target population.

The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with sodium chloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

VI. REVISION DATE

23/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5377/1/DC to IE/H/0786/1/DC			