IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Sodium chloride 5 mmol/ml Oral Solution
Sodium chloride
PA22697/015/001

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

This product was initially authorised under procedure number UK/H/5719/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 15/05/2019 under procedure number IE/H/0921/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/015/001
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 Sodium chloride 5mmol/ml Oral Solution (PL 39307/0028; UK/H/5719/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Ireland as a Concerned Member State (CMS).

This product is subject to medical prescription (legal status POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10a of Directive 2001/83/EC, as amended, as an application for a product containing an active substance of well-established use.

Sodium chloride 5mmol/ml Oral Solution is indicated for the treatment of sodium chloride deficiency.

The product contains the active substance sodium chloride. 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.

Sodium chloride 5mmol/ml oral solution provides a source of sodium (in the form of sodium chloride) where a deficiency exists.

No new clinical or 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.

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

The RMS and CMS considered that the application could be approved at the end of procedure on 03 October 2018. After a subsequent national phase, a licence was granted in the UK on 24 October 2018.

II. QUALITY ASPECTS

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II.1 Introduction

Sodium chloride 5mmol/ml oral solution is a clear, colourless solution. Each ml of oral solution contains 5 mmol (292.2 mg) of sodium chloride.

Other ingredients consist of the pharmaceutical excipient, purified water.

The finished product is packaged in amber polyethylene terephthalate bottles. The closure is a tamper-evident, child-resistant plastic cap which consists of a polypropylene inner, polyethylene outer and an expanded polyethylene liner.

The product is packaged in pack sizes of 100 ml and 300 ml. Not all pack sizes may be marketed.

The 100 ml pack size comes with either a 1 ml polypropylene oral syringe with 0.01ml graduation marks and an adaptor for the syringe, or a 4 ml oral pipette with 0.1 ml graduation marks.

The 300 ml pack size comes with a 4 ml oral pipette with 0.1 ml graduation marks.

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

rINN:	Sodium Chloride
Chemical name:	Sodium Chloride
Structure:	Simple ionic compound
Molecular formula:	NaCl
Molecular weight:	58.44
Appearance:	White or almost white, crystalline powder or colourless crystals, or white or almost white pearls
Solubility:	Freely soluble in water and practically insoluble in anhydrous ethanol

All aspects of the manufacture and control of the active substance, sodium chloride, from its starting materials 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 safe, efficacious oral solution containing 5 mmol per ml sodium chloride.

A satisfactory account of the pharmaceutical development has been provided.

The excipient purified water complies with its European Pharmacopoeia (Ph. Eur.) monograph. No materials of animal origin have been used in the preparation of this product. This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using three production scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the products

Stability studies were performed, in accordance with current guidelines, on batches of the finished product in the packaging proposed for marketing.

The results from these studies support a shelf life of 12 months, with no special storage conditions. The 100ml pack size should be discarded after 30 days of first opening. The 300 ml pack size should be discarded after 60 days of first opening.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Sodium chloride 5mmol/ml Oral Solution.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of sodium 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)

The Marketing Authorisation Holder has provided adequate justification for not submitting an ERA. Since sodium chloride oral solution is intended for generic substitution, this will not lead to an increased exposure to the environment. Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from the need for environmental risk assessment because they are unlikely to result in significant risk to the environment. The drug product is sodium chloride solution, which is an electrolyte, and therefore the applicant has not provided an environmental risk assessment. An environmental risk assessment is not deemed necessary.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Sodium chloride 5mmol/ml Oral Solution.

IV. CLINICAL ASPECTS

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IV.1 Introduction

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

IV.2 Pharmacokinetics

Sodium chloride from oral solution is rapidly and completely absorbed from the gastrointestinal tract; the peak absorption being achieved within 30 minutes of administration.

The distribution of sodium varies according to tissues: it is fast in muscles, liver, kidney, cartilage and skin; it is slow in erythrocytes and neurones; it is very slow in bone. Sodium is predominantly excreted by the kidney, but there is extensive renal tubular reabsorption mainly across the proximal tubule.

The kidneys are the major regulator of sodium and water balance. Along with hormonal control mechanisms (renin-angiotensin-aldosterone system), anti-diuretic hormone and natriutic hormone are primarily responsible for keeping the volume of extracellular space constant and regulating its fluid composition. Chloride is exchanged for bicarbonate in the renal tubules and is thus involved in the regulation of the acid-base balance.

IV.3 Pharmacodynamics

Sodium

Sodium is the principal cation in the extracellular fluid and is partly responsible for the maintenance of the extracellular fluid volume and osmolarity. In addition, sodium is involved in cell functions including nerve conduction, muscle contraction, acid-base balance, renal function and cell nutrient uptake.

The range of normal concentration of sodium in plasma is within 135 to 145 mmol/L. Sodium homeostasis is complex and closely associated with fluid balance. The total body sodium content is regulated by renal sodium excretion, which can vary widely depending on dietary intake. Various mechanisms are involved in controlling renal sodium excretion including the renin-angiotensin system, glomerular filtration rate, and natriuretic factors. A reduction in extracellular fluid volume leads to the production of angiotensin II which stimulates the secretion of aldosterone. Aldosterone promotes the

reabsorption of sodium ions by the distal tubules. There may be significant effects on sodium homeostasis in adrenal insufficiency or if mineralocorticoid excess disturbs this mechanism.

Chloride
Chloride is mainly an extracellular anion found in low concentration in bone and high concentration in some components of connective tissue such as collagen. Intracellular chloride is in high concentration in red blood cells and gastric mucosa. The balance of anions and cations are regulated by the kidney. Reabsorption of chloride generally follows reabsorption of sodium.

IV.4 Clinical efficacy
Sodium chloride is used in the management of deficiencies of sodium and chloride ions in uncompensated salt-losing conditions (e.g. diarrhoea, vomiting, renal disorders or excessive use of diuretics). Treatment is usually by intravenous saline infusion following the hospitalisation of the patient. However, the extent of the problem is much wider. For example, persons in certain climates or occupations such as miners, seamen, or the armed forces serving in warmer climates may experience persistent salt and water depletion. Similarly, chronic sodium depletion is a common problem in children with cystic fibrosis due to increased sweating seen in these patients.

Until the emergence of Slow Sodium tablets, little sodium was administered orally. Sodium chloride 5 mmol/mL oral solution contains 5 mmol of sodium chloride per mL. In which case, 2 mls of this solution contains the same amount of sodium chloride as one Slow tablet containing 600 mg sodium chloride (equivalent to 10 mmol sodium and chloride; Slow Sodium SmPC). The current formulation as an oral solution provides a suitable alternative to the use of sodium chloride tablets, particularly in young children and those with cystic fibrosis.

It has been noted that up to 95% of patients with cystic fibrosis have hyponatraemia. Infants with cystic fibrosis can develop episodes of hyponatraemic hypochloremic dehydration with alkalosis when they sweat excessively. A study showed that the incidence of metabolic alkalosis with hypoelectrolytaemia was relatively common in children with cystic fibrosis.

The concentration and dosage of sodium chloride oral solution is determined by several factors including the age, weight, and clinical condition of the patient and in particular the patient's hydration state. It is not practical to treat chronic sodium depletion, such as that occurring in cystic fibrosis, with intravenous sodium solution.

With regard to the current sodium chloride oral solution dose administration, the current UK (BNF) treatment regimen recommendation of 1-2 mmol/kg per day has been adopted. However, a study notes that the required level of sodium supplementation may be higher, and as such, the requirements need to reflect the condition of the particular patient.

No formal dosing 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. The proposed dosing regimen is acceptable despite lack of data to support the exact dosing schedule.

IV.5 Clinical Safety
Adverse events of sodium salts are attributable to electrolyte imbalances caused by excess sodium.

The main safety concern associated with the treatment of hyponatraemia concerns over-rapid administration and over-correction of sodium serum levels. In such cases, there is an osmotic shift of water out of the body's cells. In the case of the brain, this can lead to the uncommon but potentially life-threatening condition known as osmotic demyelination syndrome, in which axonal damage occurring in characteristic pontine areas can give rise to features such as quadriparesis and cognitive changes. This syndrome is a serious, sometimes fatal, demyelinating disorder of the central nervous system that all

forms of sodium chloride: hypertonic saline, isotonic saline, sodium chloride given orally, and even water restriction alone, have been causally associated with. The risk of hypernatraemia or overhydration with oral rehydration solution is low in patients with normal renal function.

Ingestion of 0.5 to 1 g/kg of sodium chloride was found to be toxic in most patients. The maximum tolerated sodium intake in adult was about 15 g. The estimated fatal amount of salt was about 1 to 3 g/kg. When serum sodium ranges between 150 and 160 mEq/l, which corresponds to 9-10 g/l of sodium chloride, central nervous system symptoms were common, and seizures occurred in approximately 10% of patients. The minimum clinically measured acute lethal serum concentration of sodium, based on the data from several handbooks, was 11000 mg/l.

The gastro-intestinal effects of oral salt administration include swollen tongue, nausea, vomiting, diarrhoea, abdominal cramps, and thirst. Neurologic effects include thirst, irritability, weakness, headache, convulsions, and coma. Cerebral edema may occur, and muscle tremors may be noted. Cardiovascular manifestations of acute hypernatraemia include both hypertension and hypotension. Tachycardia, cardiac failure, and peripheral edema may develop. Pulmonary edema and respiratory arrest may occur. Oral administration of concentrated salt solutions caused irritation of the oro-gastric mucosa. Frequent high salt intake can potentiate the risk of developing musculoskeletal problems. Data suggests that high sodium chloride intake during immobility, to an even greater extent than in ambulatory test subjects, enforces disuse-induced bone and protein losses. Since the adverse event data are derived from reference information on other sodium chloride preparations and the literature, the frequencies likely to arise with the current oral solution are not yet known.

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.

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

The applicant has submitted a risk management plan (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 Sodium chloride 5mmol/ml Oral Solution.

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

Summary of safety concerns	
Important identified risks	• Hypernatraemia and conditions that increase the risk of hypernatremia (post-operative use, impaired cardiac, or renal function) • Hypertension • 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) • Overdose
Important potential risks	• Dehydration • Conditions associated with sodium retention (such as hypertension, heart failure, peripheral

	and pulmonary oedema, renal impairment, and pre-eclampsia). • Medication Error • Use in elderly • Use in pseudohyponatraemia
Missing information	• Use in patients with cystic fibrosis • Use in young patients • Safety of long-term use • Safety in neonates, children and patients with renal and hepatic impairment

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Sodium chloride 5mmol/ml Oral Solution.

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.

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATIONS

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sodium 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.

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/5719/1/DC to IE/H/0921/1/DC			