LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Natriumklorid Evolan
(sodium chloride)

Asp no: 2014-0066

This module reflects the scientific discussion for the approval of Natriumklorid Evolan. The procedure was finalised at 2014-12-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for Natriumklorid Evolan, 500 mg, capsule, hard. The applicant applies for a marketing authorisation in Sweden through a National Procedure. The application is submitted in accordance with Article 10a of Directive 2001/83/EC, so-called well-established use (WEU) application. For a WEU application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use.

In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature.

The active substance is sodium chloride. Maintenance of sodium homeostasis requires a balance between intake and excretion of sodium.

The approved indication is as follows:

- *Symptomatic, chronic, euvolemic hyponatremia when the efficacy of fluid restriction and / or diuretic therapy (e.g., inadequate ADH secretion, SIADH) is inadequate.*

- *Hypovolemic hyponatremia (following bowel resection e.g. ileostomy / jejunostomy)*

II. QUALITY ASPECTS

II.1 Introduction

Natriumklorid Evolan is presented in the form of capsules containing 500 mg of sodium chloride which corresponds to 192 mg sodium . The excipients are magnesium stearate, colloidal anhydrous silica and gelatine. The capsules are packed in PVC-PE-PVDC / Al foil blister.

II.2 Drug Substance

Sodium chloride has a monograph in the Ph Eur.

Sodium chloride is fine-grained, white crystals which are freely soluble in water. The structure of sodium chloride has been adequately proven and its physico-chemical properties sufficiently described. The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits have been justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Natriumklorid Evolan, capsule is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin except for gelatine, which is bovine. TSE certificates have been provided for gelatine.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30 °C.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered to be adequate. There are some deficiencies in the non-clinical overview but these are considered to be superseded by the long clinical experience and use of sodium chloride.

III.2 Ecotoxicity/environmental risk assessment

An environmental risk assessment is not required for electrolytes according to Guideline because they are unlikely to result in significant risk to the environment. Natriumklorid Evolan contains no components that result in additional hazard to the environment. Natriumklorid Evolan is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

No new animal or in vitro studies have been performed with Natriumklorid Evolan. This is acceptable since the use of sodium chloride is well established in the clinic.

IV. CLINICAL ASPECTS

IV.1 Introduction

The active compound of Natriumklorid Evolan, sodium chloride, is an essential nutrient for the normal functioning of the body. It is important for nerve conduction, muscle contraction, correct osmotic balance of extracellular fluid and the absorption of other nutrients.

IV.2 Pharmacokinetics

There are no pharmacokinetic data in this application for Natriumklorid Evolan capsules which is acceptable considering that the active compound is sodium chloride. Sodium chloride is

absorbed in the whole GI-tract following oral administration. Renal excretion of the electrolytes is the main route of elimination but also to less extent *via* faeces and sweet. Serum electrolyte levels will have to be monitored in cases of renal and metabolic disorders.

IV.3 Pharmacodynamics

In adult humans, total body weight (based on an average 70-kg male) consists of 55%-65% water. Intracellular fluid accounts for slightly less than two thirds of total body water (TBW), and extracellular fluid (ECF) accounts for slightly more than one third of TBW. Of the ECF, roughly 75% is interstitial fluid and 25% intravascular fluid, or blood). In the body, water and sodium homeostasis consists of the interaction between body water, the primary determinant of ECF, and sodium, a primary and vital constituent in cellular metabolism.

Serum sodium is maintained within narrow limits (135-146 mEq / L) by several mechanisms. The two most important mechanisms are the glomerular filtration rate (GFR), which affects the number of sodium ions that pass from the glomerular capillaries into Bowman's capsule and the renal tubules, and the release of aldosterone by the adrenal glands, which increases the reabsorption of sodium by the distal nephron.

Hyponatremia is defined as a serum sodium level of < 135 mEq / L and is considered severe when the serum level is below 125 mEq / L. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, and (if severe) seizures and coma. In mild cases hyponatremia is asymptomatic, but symptoms develop as the plasma sodium level drops below 130 mmol / L. Symptoms include headache, vomiting, swollen hands and feet, restlessness, confusion, wheezy breathing and fatigue, and if undiagnosed or improperly treated can lead to seizure, coma, brainstem herniation, respiratory arrest and death. Overt neurologic symptoms most often are due to very low serum sodium levels (usually < 115 mEq/L), resulting in intracerebral osmotic fluid shifts and brain oedema. The condition of low plasma sodium concentration and osmolarity can lead to cerebral oedema, pulmonary oedema, and death.

Correction of hyponatremia must take into account the chronicity of the condition. Acute hyponatremia (duration < 48 h) can be safely corrected more quickly than chronic hyponatremia. Correction of serum sodium that is too rapid can precipitate severe neurologic complications. Most individuals who present for diagnosis, versus individuals who develop it while in an inpatient setting, have had hyponatremia for some time, so the condition is chronic, and correction should proceed accordingly.

IV.4 Clinical efficacy

The two approved indications represent specific types of hyponatremia that can have different underlying causes and by extension of the causative mechanism, have different level of severity of the hyponatraemia. Although sodium chloride has been used for decades to treat hyponatraemia, guidelines for managing hyponatraemia are based on retrospective studies and expert opinion since no prospective studies exist, presumably as the molecule is a common electrolyte. A number of publications, reviews and guidelines do however provide evidence based information regarding safety, efficacy and posology guidelines.

No exact posology exist as each patient is evaluated individually and their medical treatment regimen depends on a number of factors, including the causative agent and type of the hyponatremia to the amount of sodium loss that the patient is experiencing as well as the general condition of the patient.

SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion)

A number of review articles on management of hyponatremia have reported that fluid restriction (less than 1 to 1.5 L per day) is the mainstay of treatment and the preferred mode of treatment for mild to moderate SIADH. The combination of loop diuretics with an oral salt administration is recommended to achieve an adequate response in patients with chronic SIADH. Loop diuretics inhibit sodium resorption in the ascending limb of Henle's loop and induce free water excretion. Moreover, the salt supplementation can counter the urinary Na^+ loss. Therefore, a loop diuretic combined with oral salt can suppress free water retention, which is the main problem of SIADH.

In one study, the authors successfully treated patients with symptoms of inappropriate secretion of antidiuretic hormone using a single oral dose of 40 mg furosemide, the principle being to induce a water diuresis while compensating for electrolyte losses by ensuring a sufficiently high salt intake or oral salt tablets. Seven out of nine patients with chronic inappropriate secretion of antidiuretic hormone were successfully treated with 40 mg furosemide daily. One patient needed 80 mg, and the remaining patient achieved only a small increase in diuresis after 40 mg furosemide; this was probably related to his low creatinine clearance. In order to maintain a salt intake high enough to compensate for the loss of urine electrolytes 3 to 6 g sodium chloride was added as tablets to the sodium-free diet in six patients. Hypokalaemia occurred in five patients but was easily corrected with either supplements of potassium chloride or a potassium-sparing diuretic. These findings add further weight to evidence that furosemide along with oral sodium chloride is a good alternative for the treatment of patients with inappropriate secretion of antidiuretic hormone who cannot tolerate water restriction.

In an attempt to standardize management, new recommendations have been developed jointly by the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP) [Spasovski G, 2014]. According to the guideline, first-line treatment for patients with SIAD and moderate or profound hyponatremia should be fluid restriction. Second-line treatments include increasing solute intake with 0.25–0.50 g/kg per day of urea or combined treatment with low-dose loop diuretics and oral sodium chloride.

Hypovolemic hyponatremia (following bowel resection e.g. ileostomy / jejunostomy)

Patients with an end jejunostomy and ileostomy often have high losses of fluid and electrolytes that can necessitate long-term oral or parenteral supplements.

In one study, the authors determined if sodium chloride capsules taken with food are as effective as a glucose electrolyte solution containing the same amount of sodium chloride. Six patients with jejunostomies and residual jejunal lengths of 105 to 250 cm took the same food and water each day for eight study days. In random order, three methods of salt replacement were tested, each over 48 hours, against a period without added salt. During the three test periods the patients took 120 mmol of sodium chloride daily, as salt in gelatine capsules, as an isotonic glucose electrolyte (280 mOsmol/kg; 30 kcal) solution, and as a glucose polymer (Maxijul) solution (280 mOsmol/kg; 200 kcal). The daily stomal output remained constant for

each patient during the four test periods but varied between patients from 0.60 to 2.84 kg (daily intestinal fluid balance 0.74 to 2.61 kg). Without a salt supplement, three patients lost more sodium from the stoma than they took in by mouth (-25, -94, and -101 mmol / day) and the mean sodium balance for all six subjects was -16 mmol (range -101 to 79) daily. Extra salt was absorbed with each form of supplement (p less than 0.05); no patient with the glucose electrolyte solution (mean 96, range 0 to 226 mmol), but one patient with the glucose-polymer solution (mean 96, range -25 to 164 mmol) and two with the salt capsules (mean 66, range -8 to 145 mmol) were in negative balance. Two patients vomited with the salt capsules. There was only a small increase in energy absorption (mean 115 kcal) with the glucose polymer solution compared with the glucose electrolyte solution. The study results concluded that patients with a high jejunostomy can thus be offered a sodium supplement either as capsules or as a glucose electrolyte solution with a sodium concentration of 120 mmol/L**.**

Guidelines for management of patients with a short bowel by Small Bowel and Nutrition Committee of the British Society of Gastroenterology recommends for management of a high output jejunostomy/ileostomy that patients with stomal losses of less than 1200 ml daily can usually maintain sodium balance by adding extra salt to the limit of palatability at the table and when cooking. When stoma losses are in the range 1200 – 2000 ml, or sometimes more, it is possible for a patient to maintain sodium balance by taking a glucose-saline solution or salt capsules. Sodium chloride capsules (500 mg each) have been effective when taken in large amounts (14/24 h). If an enteral feed is given, sodium chloride needs to be added to make the total sodium concentration of the feed 100 mmol/L while keeping osmolality near to 300 mosmol/kg.

Summary
Based on the review of the literature concerning the two indications of this application and the recommendation of the various guidelines, it is acknowledged that sodium chloride supplementation is an acceptable and recommended treatment for hyponatraemia in clinical and outpatients. Each patient is an individual case and a number of factors will influence the treatment regime each patient will receive. Sodium chloride capsules are a safe method of delivery and its efficiency in absorption from the GI tract is similar to other formulations and regimes.

The applicant has provided a literature review and sufficient references to substantiate the clinical efficacy of sodium chloride in the application.

IV.5 Clinical safety

Small doses of oral sodium chloride are unlikely to cause serious short-term adverse effects.

Sodium chloride intake should be restricted in impaired renal and liver function, cardiac failure and hypertension. Sodium chloride is contraindicated in severe renal impairment (with oliguri/anuri), incompensated cardiac failure, decompensated liver cirrhosis, generalized oedema and toxaemia of pregnancy.

Excessive intake of sodium chloride can result in hypernatraemia. An overdose of sodium chloride has potential serious adverse effects. An ingestion of 0.5 to 1 g sodium chloride per kg can be toxic to fatal to most patients. Central nervous system signs and symptoms are common above 150 to 160 mmol/L. Signs and symptoms of hypernatraemia due to overdose include**:**

- Cardiovascular - tachycardia, hypertension/hypotension, fluid retention with cerebral and peripheral oedema
- Respiratory - fluid retention may produce pulmonary oedema leading to respiratory arrest
- Neurologic – headache, restlessness, irritability, dizziness, reduced salivation, seizures and coma. Hyperosmolarity of cerebral fluids may lead to irreversible neurologic damage
- Gastrointestinal- vomiting, diarrhoea, abdominal cramps, swollen tongue, and thirst

Management of overdose should be directed at restoring normal osmolality and fluid volume.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Beneficial effects
According to some original studies, review articles and formal guidelines, oral sodium chloride is possible to use in the proposed indications.

It is acknowledged that oral sodium chloride is used in the EU since over 10 years.

Unfavourable effects
Small doses of oral sodium chloride are unlikely to cause serious short-term adverse effects. Treatment of some types of hyponatreamia with sodium chloride capsules, too rapid correction of hyponatremia or an overdose are likely to have serious consequences.

Overdose of sodium chloride may cause tachycardia, hypertension/hypotension, fluid retention with cerebral and peripheral oedema, pulmonary oedema leading to respiratory arrest, headache, restlessness, irritability, dizziness, reduced salivation, seizures and coma. Hyperosmolarity of cerebral fluids may lead to irreversible neurologic damage. Vomiting, diarrhoea, abdominal cramps, swollen tongue, and thirst may occur.

Benefit-risk balance
Hyponatreamia is a common condition with numerous possible underlying causes. Sodium chloride capsules are used based on clinical experience in the proposed indications. The dosage required and dose-response is individual in each patient. Hyponatraemia must be

monitored closely to prevent excessive correction. The information in the SmPC is acceptable.

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. The language used for the purpose of user testing the PIL was Portuguese.
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.

Recommendation
The risk/benefit ratio is considered positive and Natriumklorid Evolan, 500 mg, capsule, hard is recommended for approval.

VI. APPROVAL

Natriumklorid Evolan, 500 mg, capsule, hard was approved in the national procedure on 2014-12-17.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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