COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Natriumpolystyreensulfonaat 1 g/g Focus, powder for suspension for oral/rectal use

(sodium polystyrene sulfonate)

NL License RVG: 125575

Date: 16 November 2021

This module reflects the scientific discussion for the approval of Natriumpolystyreensulfonaat 1 g/g Focus. The marketing authorisation was granted on 9 April 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic kidney disease
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
ECG	Electrocardiogram
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
IARC	International Agency for Research on Cancer
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
mEq	milli-equivalent
PD	phenolphthalein plus docusate
PfS	Powder for Suspension
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RAAS-I	renin-angiotensin-aldosterone system
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPS	Sodium Polystyrene Sulfonate
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Natriumpolystyreensulfonaat 1 g/g Focus, powder for suspension for oral/rectal use, from Focus Care Pharmaceuticals B.V.

The product is indicated for treatment of hyperkalaemia in acute and chronic renal impairment. It can also be used as a supportive therapy in patients treated with chronic haemodialysis or chronic peritoneal dialysis.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of Resonium A. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety. Sodium Polystyrene Sulfonate 400 g Powder for Suspension has been used in man more than four decades for the treatment of hyperkalaemia and it can be considered as a well-established use product. Therefore, the article 10a of the Directive 2004/27/EC is applicable.

II. QUALITY ASPECTS

II.1 Introduction

Natriumpolystyreensulfonaat 1 g/g Focus, powder for suspension for oral / rectal use is a beige to brown powder for oral / rectal suspension with a vanilla scent. Every gram of the powder contains as active substance 997.5 mg sodium polystyrene sulfonate.

The powder is packed in a HDPE jar with a sealed polypropylene screw-cap and is co-packaged with a polypropylene measuring spoon. (one levelled measuring spoon = 15 grams)

The excipient for Natriumpolystyreensulfonaat 1 g/g Focus is vanilla aroma (contains sodium benzoate (E211)).

II.2 Drug Substance

The active substance is sodium polystyrene sulfonate, an established active substance described in the European Pharmacopoeia. The active substance is an almost white or light brown, amorphous powder, practically insoluble in water, in ethanol (96 percent) and in methylene chloride. Polymorphism and stereochemistry are not known for this active substance.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The synthesis route for sodium polystyrene sulfonate consists of two chemical steps and one isolated intermediate with subsequent purification steps. The manufacturing process is performed in the absence of organic solvents and metal catalysts.

Quality control of drug substance

The drug substance specification of the MAH is according the Ph. Eur. Monograph with additional tests for microbiological quality and particle size distribution. The methods for testing microbial quality and particle size distribution are according to the Ph Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for 17 production scaled batches stored at 25°C/60% RH (60 months) and three production scaled batches stored at 40°C/75% RH (12 months). The batches were stored in container closure system that simulates the packaging used for storage and distribution (i.e. double polyethylene lined kegs). Sodium polystyrene sulfonate is very stable, no significant changes are seen under any of the conditions tested. Results of stress studies confirmed that there are no degradation impurities at these stress conditions (thermal, humidity, acidic, alkaline, and oxidizing conditions). The proposed retest period of five years and storage conditions 'Store in airtight closed original container, no special temperature storage conditions are required' are justified.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The proposed product was first registered in Spain in 1968 and has a very simple composition and formulation and is a straightforward copy of the innovator product at that time (Resonium A) from Sanofi. Both Resonium A and the proposed product comprise 99.8 to 99.9% of active substance and a small amount of vanillin flavour. The drug substance complies with the Ph. Eur. Monograph, including the requirement for potassium exchange capacity. The information on the posology and method of administration of the drug product, including preparation of the suspension for oral or rectal administration, (SPC sections 4.2 and 6.6) is the same as in the SPC of Resonium A.

A study has been performed to investigate the sameness of sodium polystyrene sulfonate. For comparison purposes, secondary standard (standardized against a primary standard), as well as a third commercial supplier have been included in this study. The batches were compared with regard to particle size distribution, bulk density, swelling index, X-ray powder diffraction, differential scanning calorimetry, thermographic analysis, content of water, sodium and water residual monomers, optical microscope analysis and in-vitro bioequivalence (i.e. potassium exchange capacity) of drug substance. From the results of the studies it can be concluded that all samples are equivalent with regard to potassium exchange capacity, regardless the small differences in their characteristics. The within product variation of test and reference as well as the speed of sedimentation of the reconstituted suspension have also been compared. Results of homogeneity and sedimentation speed were found very similar in the test and reference products analysed.

Manufacturing process

The manufacturing process exists of sieving, mixing and packaging. The product is manufactured using conventional manufacturing techniques. Because recently a seal and packaging of the measuring spoon inside the primary container has been introduced, the process has been re-validated with three pilot-scale batches manufactured with active substance from a previous supplier. This validation is appropriate. Full scale validation will be done on the first three full scale batches. An appropriate validation protocol has been provided. As the manufacturing process is a standard manufacturing process, this approach is acceptable.

Control of excipients

The excipient complies with the Ph. Eur. It is well known and the specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, assay sodium, exchange capacity, uniformity of mass of delivered doses from multidose container, loss on drying, lead and microbiological quality. The release and shelf-life requirements/limits are acceptable. The analytical methods have been adequately described and, where relevant also validated. Results of forced degradation show that purity and exchange capacity is not impacted by the tested stress conditions. Moisture content of the drug product has a slight impact on exchange capacity due to impact on the percentage active substance in one measuring spoon. Batch analytical data from the proposed production site have been provided on three full scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for six pilot-scaled batches (three batches with active substance from the current and previous supplier) stored at 25°C/60% RH (up to four years), 30°C/65% RH (one year) and 40°C/75% RH (six months) The conditions used in the stability studies are according to the ICH stability guideline and the batches were stored in the proposed commercial packaging. A slight increase in loss on drying is observed over six months storage at accelerated storage conditions and 12 months storage at long-term conditions for the batches manufactured with active substance from previous supplier. In general the results

are low and amply comply. Results of sodium assay and exchange capacity show variation, but no clear trend. In view of the provided results, the proposed shelf-life of five years, without a specific storage condition is acceptable.

In-use stability have been performed with the three pilot batches manufactured with active substance from the current supplier. Trends observed are an increase of loss on drying and an increase of total aerobic microbial count. Yet, all results amply comply. The proposed in-use shelf-life of 30 days is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Natriumpolystyreensulfonaat 1 g/g Focus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

III.1.1 Primary pharmacodynamics
Sodium polystyrene sulfonate is a cation-exchange resin that can exchange either cations or anions in contact with a solution (Scherr et al., 1961).

Studies in vitro (NG et al., 1990) with 1 g of sodium polystyrene sulfonate and a preparation consisting of sodium 13.1 milli-equivalent (mEq)/l, potassium 48.4 mEq/l and calcium 20.3 mg% showed that after two hours of contact the potassium dropped from 48.4 to 15.8 mEq/l and the calcium was reduced from 20.3 mg% to 0.8 mg%, but the sodium increased from 13.1 mEq/l to 37.2 mEq/l (indicating that the resin gives up sodium ions during the interchange) and that this interchange remained unaltered during the 24 hours of the study. These studies showed that the bond of the ion to the resin depends on three factors, namely:

- Order of affinity of the biologically active ions: hydrogen < sodium < potassium = (ammonium) < magnesium < calcium;
- Concentration of the ion to which the resin is exposed;
- Duration of the exposure of the resin to the ions in solution.

One gram of the resin has an in vitro exchange capacity of about 3.1 mEq of potassium (Mc Evoy, 2012). This cation-exchange capacity by the resin of Sodium polystyrene sulfonate has

been confirmed in other nonclinical studies (Watling et al., 1995; Linakis et al., 2001; Rivard et al., 2004; Martí Bonmati et al., 2008).

It has been demonstrated in nonclinical studies that Sodium polystyrene sulfonate binds potassium and lithium, with a preference between both cations for potassium (Watling et al., 1995), and that potassium repletion did not interfere with the ability of sodium polystyrene sulfonate to lower serum lithium concentration in animals experimentally poisoned with lithium (Linakis et al., 2001). Several studies have demonstrated that sodium polystyrene sulfonate also can be used in vitro to reduce the potassium content of enteral nutrition formulas (Rivard et al., 2004; Martí Bonmati et al., 2008).

III.1.2 Secondary pharmacodynamics

The cation exchange resin sodium polystyrene sulfonate has proved useful in lithium overdosage, both in vitro (Watling et al., 1995) and in studies in animals (Linakis et al., 1992; Linakis et al., 1995). In addition, Watling et al. (1995) using in vitro solutions observed that increasing concentrations of sodium polystyrene sulfonate bound more lithium, whereas changes in pH had little effect on lithium binding. Nonetheless, it is noted that potassium is preferentially bound to Sodium polystyrene sulfonate over lithium.

Sodium polystyrene sulfonate has also showed ability to bind iron from ferrous sulphate solutions (O'Connor et al., 1996). The authors performed a series of in vitro experiments in which various concentrations of iron and sodium polystyrene sulfonate were combined and free ferrous iron was measured with the use of a colorimetric assay. The iron binding by sodium polystyrene sulfonate was depending on the pH, being lower at pH 7 (97%) than at pH 2 (98%).

The potential application of ion-exchange resins for the enhancement of intranasal immune response to influenza HA vaccine has been evaluated by Higaki et al. (1998). The authors immunized intranasally female balb/c mice with inactivated influenza HA vaccine and one of four kinds of resin microparticles: sodium polystyrene sulfonate, calcium polystyrene sulfonate, polystyrene benzyltrimetylammonium chloride, or polystyrene divinylbenzene. The results demonstrated that intranasal administration of influenza HA vaccine in combination with the 20-45 microns sized particles of sodium polystyrene sulfonate resin induced the highest levels of mucosal IgA, and enhanced systemic haemagglutinin-inhibiting antibodies. Furthermore, mice intranasally immunized with HA vaccine together with sodium polystyrene sulfonate resin showed higher protection against viral challenge than those that received HA vaccine alone. The authors suggest that intranasal administration of influenza HA vaccine with sodium polystyrene sulfonate resin might be both a safe and an effective means of immunization.

III.1.3 Safety Pharmacology

No safety pharmacology issues are to be expected from a non-clinical point of view for the central nervous-, cardiovascular- and respiratory systems, because of the very low bioavailability of the resin.

III.1.4 Pharmacodynamic drug interactions

Information concerning the interactions of the sodium polystyrene sulfonate and other substances or products comes mainly from the experience of use of the product in humans.

Ayoub *et al.* conducted a study of sodium polystyrene sulfonate with and without sorbitol in rats. This study involved a total of 26 Sprague-Dawley rats weighing 200 to 250 g which underwent 5/6 nephrectomy. They were divided into six groups, and were given enema solutions under anesthesia (normal saline, 33% sorbitol, 33% mannitol, sodium polystyrene sulfonate in 33% sorbitol, sodium polystyrene sulfonate in normal saline, and sodium polystyrene sulfonate in distilled water). Study results showed that one rat from the sorbitol and one from the mannitol group had foci of ischemic colonic changes. The rats receiving sodium polystyrene sulfonate enema, in sorbitol, normal saline, distilled water, had crystal deposition with colonic necrosis and mucosal erosion. All the rats not given sodium polystyrene sulfonate survived until sacrifice at 48 hours whereas 11 of 13 rats that received sodium polystyrene sulfonate sorbitol, normal saline or distilled water died or were clearly dying and sacrificed sooner. There was no difference between sorbitol and mannitol when given without sodium polystyrene sulfonate. It was concluded that in the uremic rat model, sodium polystyrene sulfonate enema given alone or with sorbitol or mannitol seemed to cause colon necrosis and high mortality rate whereas 33% sorbitol without sodium polystyrene sulfonate did not (Ayoub et al., 2015). *Abuelo and colleagues* reviewed the therapy of severe hyperkalemia with sodium bicarbonate, sodium polystyrene sulfonate, and hemodialysis with low potassium dialysate, measures that have been used since the 1940s. The author stated in this review that intestinal necrosis, usually of the colon, is an infrequent, but often fatal complication of sodium polystyrene sulfonate (Abuelo, 2018).

The role of sodium polystyrene sulfonate in producing intestinal necrosis is based on three types of evidence. The first involves studies in rats. In one study, rats given 10 ml enemas with 70% sorbitol, which is 47 times the dose used in humans, developed colonic necrosis, whereas enemas of sodium polystyrene sulfonate at 23 times the human dose had no toxic effect. In contrast, in a more recent study, only one of five rats given enemas with 33% sorbitol had necrosis, but of the eight rats given sodium polystyrene sulfonate enemas, six were dead or dying, and three had mucosal ulcerations, although the dose was only one-quarter the dose of the previous study. Both studies found that rats given sodium polystyrene sulfonate in sorbitol developed colonic necrosis, but the earlier study ascribed it to sorbitol, whereas the later study ascribed the necrosis to sodium polystyrene sulfonate. Although these results are concerning for intestinal toxicity of sodium polystyrene sulfonate and sorbitol, the use of doses many times the human dose and the contradictory findings between the two rat studies cast doubt on the clinical application of these reports. The other two types of evidence are found in clinical studies and will be discussed in section IV of this report.

III.2 Pharmacokinetics

III.2.1 Absorption

Sodium polystyrene sulfonate is not absorbed by the gastrointestinal tract (Micromedex, 2012). Sodium polystyrene sulfonate characteristics such as its insolubility in water and its high molecular weight prevent the substance from the absorption in the gastrointestinal tract. The onset of action has been reported to occur one to two hours after administration (Allon,

1995) or in a wider range of 2-24 hours (Micromedex, 2012). A continuous effect has been documented, even up to 24 hours after administration is ceased (Scherr et al., 1961).

III.2.2 Distribution

Since sodium polystyrene sulfonate is not absorbed, the distribution of the resin is limited to the gastrointestinal tract (Micromedex, 2012).

III.2.3 Metabolism

As for previous pharmacokinetic data, the pharmacokinetic behaviour of sodium polystyrene sulfonate is mainly known from its use in man. Digestive fluids have no effect on sodium polystyrene sulfonate. It is not metabolized (Micromedex, 2012). During its pass through the colon it exchanges the majority of its sodium ions for potassium ions, whereas the resin remains inalterable. If the resin is administered in the form of enema, it should be retained for as long as possible (at least nine hours).

III.2.4 Excretion

The pharmacokinetic behaviour of sodium polystyrene sulfonate is mainly known from the use in man. The resin is 100% eliminated in the faeces together with the potassium ions, thus reducing the serum level of potassium (Micromedex 2012). Approximately 1 mEq of potassium is excreted for each gram of resin used (Kunis and Lowenstein, 1981).

III.2.5 Pharmacokinetic drug interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. Several nonclinical studies in mice or in vitro using stock solutions of lithium which were added to fixed amounts of sodium polystyrene sulfonate demonstrate the binding between lithium and sodium polystyrene sulfonate. This interaction involves a decrease in the lithium absorption (Watling et al., 1995; Linakis et al., 1992; Linakis et al., 1995). Sodium polystyrene sulfonate has also proved ability to bind iron from ferrous sulphate solutions, added to sodium polystyrene sulfonate, decreasing its absorption, in a nonclinical in vitro study (O'Connor et al., 1996). Sodium polystyrene sulfonate also reduces the absorption of levothyroxine (Sweetman, 2012). An in vitro study found that when levothyroxine 200 µg was dispersed in 100 ml water with 15 g sodium polystyrene sulfonate, the concentration of the levothyroxine fell by 93% at pH 2 and by 98% at pH 7 (McLean et al.,1993).

III.3 Toxicology

III.3.1 Single dose toxicity

Table 1. Acute toxicity for Sodium polystyrene sulfonate

Organism	Test type	Route	Reported dose (normalized dose)	Effect	Source
mouse	LD50	oral	>10125 mg/kg (10125 mg/kg)		ChemIDplus Advanced, 2012
mouse	LD50	intraperitoneal	>6750 mg/kg (6750 mg/kg)		ChemIDplus Advanced, 2012
mouse	LD50	subcutaneous	>15 g/kg (15000 mg/kg)		ChemIDplus Advanced, 2012
rat	LC50	inhalation	2600 mg/m^3/4h (2600 mg/m^3)	lungs, thorax, or respiration: respiratory obstruction	ChemIDplus Advanced, 2012
rat	LD50	oral	>8 g/kg (8000 mg/kg)		ChemIDplus Advanced, 2012
rat	LD50	intraperitoneal	>6 g/kg (6000 mg/kg)		ChemIDplus Advanced, 2012
rat	LD50	subcutaneous	>15 g/kg (15000 mg/kg)		ChemIDplus Advanced, 2012

III.3.2 Repeat-dose toxicity

The toxicity information of sodium polystyrene sulfonate refers basically to the use in man and recognized and scientific literature.

A toxicity study performed in rats by Lillemoe et al. (1987) investigated the effects of sodium polystyrene sulfonate-sorbitol enemas in an experimental model using both normal and uremic rats. The authors studied two groups of Sprague-Dawley rats. One group was made uremic by performance of bilateral nephrectomy, whereas the other group underwent sham operation. The rats were administered enemas of saline, sodium polystyrene sulfonate alone, sorbitol alone, or sodium polystyrene sulfonate in sorbitol. In non-uremic rats, significant pathologic changes (transmural necrosis) only were noted in the rats receiving sorbitol or Sodium polystyrene sulfonate in sorbitol enemas. In uremic rats, extensive transmural necrosis was noted in all rats receiving enemas of sorbitol or sodium polystyrene sulfonate in sorbitol. These rats died within the period of observation compared with no deaths in the rats that received enemas without sorbitol. The authors considered that two facts were apparent from these experiments: (1) sorbitol (not the sodium polystyrene sulfonate) was responsible for the colonic damage, and (2) damage from sorbitol enemas was potentiated in uremic rats. The detailed pathogenesis of the damage is not known, but it may be speculated that the osmotic load from sorbitol enemas causes vascular shunting resulting in colonic ischemia. Alternatively, concentrated doses of sorbitol may cause directed toxic damage. Worsening of colonic pathology in the uremic rats is especially interesting, since most of the reported clinical cases have been in patients with severe renal disease. In renal disease, the rennin-angiotensin system is disordered with mesenteric vascular instability, and thus the intestinal vasculature of the patients may be particularly vulnerable to an osmotic load.

III.3.3 Genotoxicity

Relevant studies in animals have not been found in literature to evaluate the genotoxic of sodium polystyrene sulfonate. Sodium polystyrene sulfonate is not classified in either of the group published by the International Agency for Research on Cancer (IARC).

III.3.4 Carcinogenicity

Relevant studies in animals have not been found in literature to evaluate the carcinogenic potential of sodium polystyrene sulfonate. Sodium polystyrene sulfonate is not classified in either of the group published by the IARC. Nevertheless, the drug has been used for decades without any reports of these type of alterations. No reports of carcinogenicity or neoplasms have been received by the MAH in the examined Periodic Safety Update Reports. Likewise, no reports of genotoxicity with sodium polystyrene sulfonate and no reports of tumour induction from substances with similar molecular structure and/or mode of action have been received.

III.3.5 Reproductive and developmental toxicity

Sodium polystyrene sulfonate is included in Classification C for gestation by the Food and Drug Administration (FDA). No clinical reproduction studies have been carried out in animals and it is not known whether it may cause foetal damage when administered during pregnancy or breast feeding.

III.3.6 Tolerance

Sodium polystyrene sulfonate is not absorbed or metabolized by the gastrointestinal tract, thus its distribution is limited to the gastrointestinal tract. The resin is totally eliminated in the faeces. Few studies have been carried out on toxicity and most correspond to the use of the product in man. The sites which come into contact with the drug as a result of the method of administration and through accidental or unavoidable exposure to the product are gastrointestinal tract and lungs.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH notes that an ERA according to CPMP guideline CPMP/SWP/4447/00 (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use) has not been provided.

Sodium polystyrene sulfonate is a very well-known medicinal product, which has been in clinical use in the EU for more than 40 years. The drug product currently marketed in France is "Kayexalate, poudre pour suspension orale et rectale", which was authorized in 1980. Therefore, the legal base of this application is a well-established use. Moreover, due to the fact that the active substance is practically insoluble in water and comparative dissolution curves cannot be carried out.

Comparing Sodium Polystyrene Sulfonate 400 g powder for suspension and Kayexalate, poudre pour suspension orale et rectale, the following observations are made:

- Both drug products have the same pharmaceutical form and are marketed in multidose containers, containing 400 g and 454 g, respectively.

- The concentration of active substance in the powder for suspension is practically the same (99.75% and 99.934%, respectively).
- The dose is the same for both products: 15 g one to four times per day.

As the target population (Chronic Kidney Disease) is known and clearly identified and taking into account that the marketing of Sodium Polystyrene Sulfonate 400 g Powder for Suspension would partially replace the use of Kayexalate, but not increase the overall consumption of active substance, it can be concluded that the approval of this medicinal product will not lead to an increased exposure to the environment.

III.5 Discussion on the non-clinical aspects

The submission is intended for well-established use. As such, the MAH has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate. The effects of sodium polystyrene sulfonate are well known, and the literature on pharmacology, pharmacokinetics and toxicology has been adequately reviewed in the MAH's non-clinical overview.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies have been performed by the MAH. These are not required for a well-established use application. The clinical pharmacology, clinical effects and safety of sodium polystyrene sulfonate are well known. Below an overview of the submitted literature data has been presented.

IV.2 Pharmacokinetics

Sodium polystyrene sulfonate is not absorbed or metabolized in the gastrointestinal tract. The distribution of the resin is limited to the gastrointestinal tract. The resin is 100% eliminated in the faeces together with the potassium ions, thus reducing the serum level of potassium. Approximately 1 mEq of potassium is excreted for each gram of resin used.

IV.3 Pharmacodynamics

Sodium polystyrene sulfonate is a cation-exchange resin that releases sodium in exchange for other cations. Following oral administration, sodium is released from the resin in exchange for hydrogen ions in the acidic environment of the stomach. As the resin passes through the intestines, hydrogen cations exchange with those cations that are in greater concentrations and the cationically modified resin is excreted in the faeces. Because of the relatively high concentration of potassium present in the large intestine, conversion of the resin to the potassium form occurs principally at this site. Following rectal administration of sodium polystyrene sulfonate, sodium ions are partially released from the resin in exchange for other cations present.

The onset of its action occurs one to three hours after administration, nevertheless, a wider onset of action of 2-24 hours has also been reported. Sodium polystyrene sulfonate has a continuous effect, even up to 24 hours after administration is ceased. In clinical use, much of the exchange capacity of sodium polystyrene sulfonate is utilized for cations other than potassium such as calcium, magnesium, iron, organic cations, lipids, steroids, and proteins. Thus, although 1 gram of the resin has an in vitro exchange capacity of about 3.1 mEq (range: 2.81-3.45 mEq) of potassium, an in vivo exchange capacity greater than 1 mEq of potassium per gram of resin is not likely.

The affinity of the potassium ion for the resin is much higher than the sodium ion and, in fact, in the presence of a high concentration of potassium ions, it liberates the sodium ion to bond to the potassium ions . This ions exchange is the basis of Sodium polystyrene sulfonate pharmacological action. The efficacy of the action is dependent on the concentration of potassium ions the resin is exposed to and the duration of the exposure of the resin to the potassium ions in solution. As the resin passes through the colon, it comes into contact with fluids containing increasing amounts of potassium. Whereas in the cecum the concentration of sodium and potassium are similar to those in the small intestine, in the stool water of the sigmoid colon there may be 6 to 38 mmol/l sodium and 14 to 44 mmol/l potassium). The result is that potassium is taken up in increasing amounts in exchange for sodium ions. The length of time the resin remains in the body is a decisive factor in its effectiveness. For this reason oral administration is more effective than the use of enemas which should, if possible, be retained for as long as possible (four to ten hours).

The bond of potassium to the resin in the gastrointestinal tract is constantly efficient. Greenman et al (1951) observed in vivo a bond efficacy of potassium with the resin of 50% higher than that of sodium, even when the diet contained an important amount of sodium. It could be assumed that this percentage would be even higher in the case of the diet with a low content in electrolytes to which patients with impaired renal function are often subjected.

IV.4 Interactions

Regarding pharmacokinetic interactions, ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine and lithium salts. These interactions could be considered pharmacokinetics because Sodium polystyrene sulfonate affects the availability (absorption) and consequently the effect of levothyroxine and lithium. Information about an interaction between levothyroxine and polystyrene sulfonates seems to be limited, but it would appear to be of general importance. Lithium is the medication of choice for the treatment of maniac-depressive disorders. Sodium polystyrene sulfonate may be useful in clinical practice for gastric decontamination after an overdose of lithium. In addition to pharmacokinetic interactions, different types of pharmacodynamic interactions for sodium polystyrene sulfonate have been described.

As stated previously, sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, it has been reported to cause metabolic alkalosis in patients with renal disease. Rectal use of sodium polystyrene sulfonate may avoid this reaction. In addition to alkalosis, the concurrent use of

aluminium hydroxide and the resins may result in intestinal obstruction due to concretions of aluminium hydroxide, , although it is not completely established. This pharmacodynamic interaction is due to the competition for binding sites without change in the plasma concentrations of the interacting drugs. Thus, as a precautionary measure, where concurrent drug therapy exists sodium polystyrene sulfonate 400 g powder for suspension Summary Products Characteristics (SmPC) recommends that the administration should be separated at least two hours.

The treatment of the hyperkalaemia in patients with impaired renal function sometimes includes the ingestion of sorbitol and a cation exchange resin. Sodium polystyrene sulfonate resins increase stool potassium excretion in normokalaemic subjects, but proportionately more potassium is excreted due to cathartics when the two drugs are combined. Cases of severe colonic necrosis have been reported after the administration of enemas containing Sodium polystyrene sulfonate and sorbitol for the treatment of hyperkalaemia, some of them with death as a result. Colonic and gastrointestinal necrosis adverse events have also been reported after oral or nasogastric administration of sodium polystyrene sulfonate with sorbitol, and there have also been reports of colonic necrosis with oral or rectal sodium polystyrene sulfonate alone.

The efficacy of sodium polystyrene sulfonate is adversely affected by combined administration with substances with a high potassium content, such as fruit purée and fruit juices. The therapeutic effect of an angiotensin-converting enzyme (ACE) inhibitor can be partially or completely lost by taking sodium polystyrene sulfonate. This is particularly relevant for patients on a salt-restricted diet.

IV.5 Clinical efficacy

IV.5.1 Introduction

Sodium polystyrene sulfonate 400 g powder for suspension (PfS) is a sulfonated cation-exchange resin belonging to the pharmacotherapeutic group V03AE01 drugs for treatment of hyperkalaemia and hyperphosphatemia.

This resin is indicated in the treatment of hyperkalaemia (Ryan, 2012; Sweetman, 2012; Micromedex 2015; Chernin, 2012).

Hyperkalaemia is characterized by a plasma potassium concentration exceeding 5.0 mEq/l (Gougoux, 2001). Hyperkalaemia results from changes in the intake of, the excretion of, and from a shift of potassium:

1. Increased intake of potassium. Hyperkalaemia is observed with the ingestion of either potassium supplements or salt substitutes, or with the intravenous administration of a bolus of potassium chloride (Gougoux, 2001).

2. Decreased renal excretion of potassium is the most frequent mechanism involved. Acute or chronic renal failure, hypoaldosteronism and potassium-sparing diuretics

(e.g., spironolactone, triamterene, amiloride) reduce the urinary excretion of potassium. Cyclosporin, trimethoprim, ACE inhibitors and angiotensin II receptor antagonists can also decrease the renal excretion of potassium. The risk of hyperkalaemia is increased by the presence of a significant renal failure, especially when a diabetic nephropathy is accompanied by hypo-reninemic hypoaldosteronism (Gougoux, 2001).

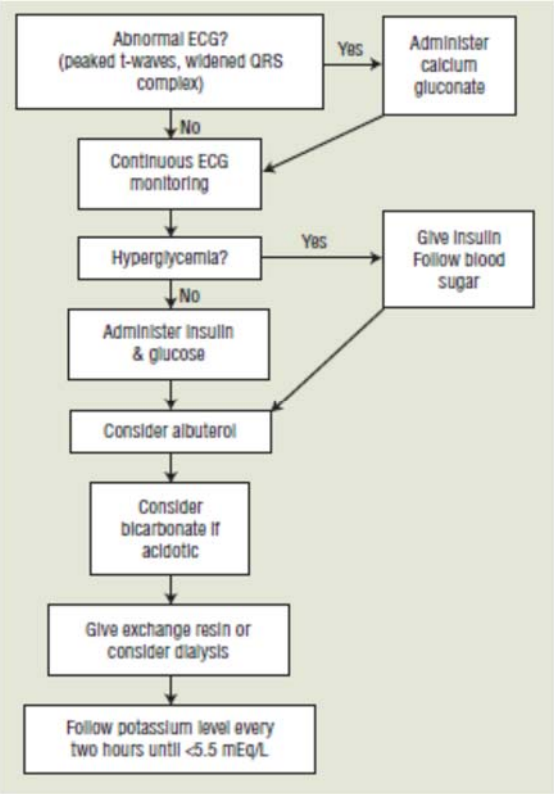
3. Extracellular shift of potassium. Because 98% of the potassium is intracellular, a shift of even small amounts of potassium from the intracellular to the extracellular compartment markedly increases kalaemia, but not the total body potassium. Accelerated transfer of potassium from the cells is observed in hyperchloremic metabolic acidosis with an excess of inorganic acids, and with the destruction of red blood cells during haemolysis and of muscle cells during rhabdomyolysis. By contrast, the cellular uptake of potassium is reduced by drugs like succinylcholine during anaesthesia and by aldosterone deficiency, insulin deficiency and beta2-adrenergic blockade (Gougoux, 2001).

Hyperkalaemia is a life-threatening electrolyte abnormality when it exceeds 6.5 mEq/L to 7.0 mEq/L or induces the characteristic electrocardiogram (ECG) changes: disappearance of P wave; widening of QRS complex; and symmetrical peaking of T wave. Once a laboratory error or pseudohyperkalaemia resulting from haemolysis, marked leucocytosis or thrombocytosis has been ruled out, an ECG should be obtained (Gougoux, 2001).

This condition is frequent in acute kidney failure. Hyperkaliaemic arrhythmias are frequent with a serum potassium level below 8 mEq/L and include significant electrocardiographic changes. Treatment must be immediate as the hyperkalaemia may cause cardiac block and death.

The general algorithm of treatment of hyperkalaemia is shown below:

Figure 2. Treatment approach for hyperkalaemia (Micromedex, 2012)



In patients who have acute ECG changes, calcium should be administered to prevent or treat any cardiac manifestations of hyperkalaemia. Once the patient is hemodynamically stabilized, the serum potassium concentration should be rapidly decreased to <5.5 mEq/L within minutes by administering drugs that cause an intracellular shift. If the patient is asymptomatic, rapid correction is not necessary. The clinician can administer an ion exchange resin (e.g., sodium polystyrene sulfonate) that results in removal of potassium from the body over several hours to days (Micromedex, 2012).

Dock (Dock, 1946) was the first to suggest the use of an ion exchange resin as a drug to reduce the amount of sodium ion available for absorption in the gastrointestinal tract in patients with congestive heart failure. Later clinical studies demonstrated that ion exchange resins, both carboxylic and sulfonic, could bond to potassium ions in the gastrointestinal tract and eliminate them through the faeces together with the resins, thus making them useful in the treatment of hyperkalaemia (Irwin et al., 1949).

Elkinton et al. (1950) administered a carboxylic ammonium cycle ion exchange resin for the treatment of hyperkalaemia by both oral and rectal route and obtained very satisfactory interchange with potassium ions resulting in a reduction of the plasma levels of potassium. To prevent the adverse effects of the cycle ammonium resin (increase of the plasma levels of urea and metabolic acidosis), Evans et al. (1953) administered a sodium cycle resin which turned out to be both faster and more innocuous in its action. Since then numerous clinical trials and studies have demonstrated the effectiveness of the sodium cycle ion exchange resin, sodium polystyrene sulfonate (Bull, 1952; Bull et al., 1953; Evans et al., 1953; Scherr et al., 1961; Flinn et al., 1961; Johnson et al., 1976; Lachaal and Venuto, 1989; Chernin et al., 2012).

Nowadays, sodium polystyrene sulfonate is a common element of therapeutic approach in the current guidelines for the treatment of *current therapeutic standards for the management of acute renal failure* (Fry and Farrington, 2006), in the *current standards of treatment of chronic kidney disease* (The VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease, 2007), in the *current therapeutic standards for the management of oliguria* (Deravajan, 2012) and in the *current paediatric standards of hyperkalaemia management in children* (Verive, 2012).

Sodium polystyrene sulfonate 400 g PfS was first authorized in Europe in the early 50s and has been in clinical use worldwide for decades. Formulations containing sodium polystyrene sulfonate are approved world-wide for the treatment of hyperkalaemia and have been widely used, in terms of both geographical and demographical extension with a good and recognized safety profile. Therefore, sodium polystyrene sulfonate can be claimed as a well-established use active substance for the intended indication. Accordingly, the present application is submitted as a complete dossier, including clinical and nonclinical data based on scientific literature.

The bibliographic review has been conducted to date using the MEDLINE, EMBASE, COCHRANE, TOXNET and related databases, likewise the recognised medical and scientific compendiums (Mc Evoy, 2012; Ryan, 2012; Sweetman, 2012 and Micromedex, 2015). The clinical studies referenced in the literature show the compliance in the correct clinical use of the product and many of them refer to patients with several grades of renal impairment including anuria, oliguria, and acute or chronic kidney disease. The target study population of most of the clinical studies and individual cases presented in the literature was adult men and women and children with hyperkalaemia. Although there is scarce scientific literature regarding the use of sodium polystyrene sulfonate, this product has been registered for commercialization for various decades and widely used. It has been observed that the safety profile is very positive and recent scientific publications demonstrate the efficacy of the product (Chermin et al., 2012). Overall, the efficacy of the treatment of hyperkalaemia with sodium polystyrene sulfonate is considered well-established taking into consideration the bibliographic data and the vast experience of the clinical use in an efficient way.

IV.5.2 Bibliographic evidence of efficacy

Sodium polystyrene sulfonate 400 g PfS is used for the treatment of hyperkalaemia. Hyperkalaemia, an abnormally raised plasma-potassium concentration, can occur if the potassium intake is increased, if the renal excretion decreases (as in renal failure or adrenocortical insufficiency), or if there is a sudden efflux of potassium from intracellular stores, (as in acidosis, or cell destruction due to tissue trauma, burns, haemolysis, or rhabdomyolysis). Renal failure is the most common cause of severe hyperkalaemia. Hyperkalaemia may also be induced by drugs such as the potassium-sparing diuretics, cyclosporine, tacrolimus, non-steroidal anti-inflammatory drugs, or ACE inhibitors. Usually the renal mechanisms for potassium excretion adapt readily to an increased potassium load, and hyperkalaemia due to increased dietary intake is rare unless renal function is also impaired. Hyperkalaemia mainly affects the heart, but skeletal muscle function may also be affected. Symptoms include ECG abnormalities, ventricular arrhythmias, cardiac arrest, and also neuromuscular dysfunction such as muscle weakness and paralysis (Sweetman, 2012).

Sodium polystyrene sulfonate is used in the treatment of hyperkalaemia. The drug aids in the removal of excess potassium from the body and should be considered an adjunct to other measures such as restriction of electrolyte intake, control of acidosis, and a high caloric diet. Before therapy is instituted, the cause of hyperkalaemia should be determined and eliminated if possible. Because the action of the resin is slow, treatments that facilitate shift of potassium into cells, such as administration of sodium bicarbonate and/or dextrose (with or without insulin), and/or other treatments (e.g., a calcium salt) are indicated in patients with hyperkalaemia evidenced by conduction defects (widening of the QRS complex or ventricular depolarisation) or arrhythmias. Sodium polystyrene sulfonate is most useful when hyperkalaemia is not life-threatening or when other measures have reduced the dangers of hyperkalaemia (Mc Evoy, 2012).

According to current therapeutic guidelines, the following recommendations should be followed:

- ***Acute renal failure:*** the use of resins is recommended as part of the treatment. Sodium polystyrene sulfonate or calcium polystyrene sulfonate are the most commonly used resins, given at an oral dose of 15 g up to thrice daily, together with an osmotic laxative. They can also be given rectally (Fry and Farrington, 2006).
- ***Chronic kidney disease:*** treatment of high levels of potassium should be guided by balancing the benefit and harm to address the most likely aetiology:
  a) Dietary restriction of potassium intake considering a consultation with a dietitian
  b) Increase urinary potassium excretion using loop diuretics in the absence of volume depletion
  c) Lower dose or withdraw angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker if the potassium is > 6 mEq/L
  d) Treating acidosis with oral sodium bicarbonate
  e) Increase faecal potassium excretion using sodium polystyrene sulfonate and
  f) Refer to nephrology if aetiology is unknown (The VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease, 2007).
- ***Oliguria:*** Serum potassium levels of 5.5-6.5 mEq/L should be treated by eliminating all sources of potassium from the diet or intravenous fluids and administration of a cation exchange resin, such as sodium polystyrene sulfonate (Deravajan, 2012).
- ***Paediatric hyperkalaemia:*** mild to moderate hyperkalaemia (potassium 6.-7.0) is treated by placing patient on monitor and giving 0.5-1 g of sodium polystyrene resin/kg of corporal weight daily in divided doses, orally or as retention enema over four to six hours (Ryan, 2012). Oral route is contra-indicated in neonates (Micromedex, 2012; Sweetman, 2012).

The following table summarises the sodium polystyrene sulfonate medicinal products indicated for the treatment of hyperkalaemia commercialized worldwide.

Table 3. Commercialized sodium polystyrene sulfonate (all Powder for Suspension)

Brand names	Routes	Manufacturer	Countries marketed
Resonium A / Resonium	Oral or rectal	Sanofi-Aventis	Australia, Austria, Denmark, Finland, Germany, Hong-Kong, Hungary, Ireland, Malaysia, The Netherlands, New Zealand, Poland, Portugal, Sweden, Switzerland, Thailand, United Kingdom

Brand names	Routes	Manufacturer	Countries marketed
Kayexalate	Oral or rectal	Sanofi-Aventis	Belgium, Canada, France, Israel, Italy, Thailand, United States, Venezuela
K-Exit	Oral or rectal	Omega	Canada
Anti-Kalium Na	Oral or rectal	Medice	Germany
Elutit-Natrium	Oral or rectal	Felgentrager	Germany
Resinsodio	Oral	Laboratorios Rubió	Spain, Thailand, Nicaragua, Cuba, Malaysia, Costa Rica and Morocco
Kexelate	Oral or rectal	Adcock Ingram Critical Care	South Africa
Kionex	Oral or rectal	Paddock	United States
Sodium polystyrene sulfonate	Oral	Carolina Medical	United States
Sodium polystyrene sulfonate with enema kit	Rectal	Carolina Medical	United States

Dock et al, 1946 was the first to suggest the use of an ion exchange resin as a drug to reduce the amount of sodium ion available for absorption in the gastrointestinal tract in patients with congestive heart failure. Later studies demonstrated that ion exchange resins, both carboxylic and sulfonic, could bond to potassium ions in the gastrointestinal tract and eliminate them through the faeces together with the resins, thus making them useful in the treatment of hyperkalaemia (Irwin et al, 1949).

Evans et al. reviewed five cases of anuria or severe oliguria complicated by hyperkalaemia treated with sodium sulfonic resin, administered both by mouth and by retention enema 15 g, three to four times/day by mouth and 30 g/day by enema. Serum potassium level satisfactorily reduced in four patients with final recovery in two. The resin is more effective in removing potassium when given orally than when given by retention enema (Evans et al, 1953). In 1953 Bull et al. reviewed the treatment and progression of three patients with hyperpotassemic paralysis which demonstrated that serum potassium level fell progressively after the administration of the cation exchange resin. Bernard et al, (1958) also described the experience of two patients with oliguria and hyperkalaemia. An exchange resin was administered by rectal route to an oliguric woman of 37 years of age with severe hyperkalaemia and of a woman of 67 years. In both cases the serum potassium levels dropped to normal levels.

Flinn et al., 1961 also proved the resin in ten oliguric patients. The ten patients were divided into three groups depending on the treatment: sorbitol, resin and sorbitol, and sorbitol and

resin as enemas. The three groups showed a gradual reduction of the level of serum potassium, but the sorbitol was only more effective than the combination of sorbitol and resin.

Scherr et al, 1961 evaluated the efficacy of 20-60 g suspended resin/day administered orally or 10-40 g resin/day by retention enema in 32 patients with acute or chronic kidney disease. Results indicated a significant reduction of plasma potassium within the first 24 hours (Scherr et al, 1961).

Gruy-Kapral evaluated six patients with end-stage renal disease receiving five different regimens (placebo; sodium polystyrene sulfonate 30g; phenolphthalein 520 mg with docusate 800 mg (PD); sodium polystyrene sulfonate 30 g plus PD and sodium polystyrene sulfonate 30 g plus sorbitol 60 g). Mean serum potassium concentrations showed increases from baseline to 12 hours after treatment with all five regimens; however, the increase with placebo was greater than for any of the other treatment protocols (Gruy-Kapral, 1998). Moreover, two individual cases also demonstrated the efficacy of sodium polystyrene sulfonate in treating hyperkalaemia.

Tak and Diamant, 1993 evaluated the treatment of 15 g/day of sodium polystyrene sulfonate administered orally in a 67-year-old woman after ileal conduit diversion. Results showed that the treatment was effective. After stopping the treatment, hyperkalaemia and hypercalcemia recurred with a later normalization of these parameters after restoring the medication (Tak and Diamant, 1993).

Moreover, a 14-year-old patient with pseudohypoaldosteronism treated with intermittent rectal calcium Resonium changed to sodium Resonium 0.25 g/kg twice daily indicated that disease improvement and control of electrolytes when treated orally while no efficacy signs were observed when treated rectally (Porter et al, 2003).

A recent study conducted by Chermin evaluated the efficacy of prevention of hyperkalaemia recurrence in 14 patients receiving a low-dose sorbitol free- sodium polystyrene sulfonate indicated that no patient developed hyperkalaemia after the resin was started. Hypernatremia were not found during the follow-up period (median length of follow-up, 14.5 months). The results demonstrated that low-dose sodium polystyrene sulfonate is effective as a secondary preventive measure for hyperkalaemia induced by renin-angiotensin-aldosterone system (RAAS-I) in chronic kidney disease (CKD) patients with heart disease (Chermin et al, 2012).

These studies and individual cases demonstrated the efficacy in the treatment and prevention of hyperkalaemia. Although there is few scientific literature regarding the use of sodium polystyrene sulfonate, it should be taken into consideration that this product has been registered for commercialization since various decades and has an excellent safety profile.
Overall,

i) the main therapeutic guidelines,
ii) the bibliography including studies evaluating the efficacy and
iii) the extensive clinical use for various decades worldwide

demonstrate that the medicinal product is efficient for the treatment and prevention of hyperkalaemia.

IV.6 Clinical safety

IV.6.1 Introduction

Sodium polystyrene sulfonate is not absorbed or metabolized in the gastrointestinal tract. The distribution of the resin is limited to the gastrointestinal tract, so it exerts its action at a local level (Micromedex, 2012). As a result, it exhibits low systemic toxicity and most common adverse events are mostly limited to the gastrointestinal tract where it displays its action. Furthermore, it is devoid of any teratogenic or carcinogenic effects.

The limiting factor for its use in clinical practice is hypernatremia, hypocalcaemia or any other circumstance that may bring this on in the patient. All cation exchange resins have the inconvenience of not being totally selective for potassium and small amounts of other cations may be exchanged during treatment. Therefore, in patients treated with sodium polystyrene sulfonate the levels of electrolytes should be monitored at regular intervals to prevent possible disorders (Berlyne, 1966; Mc). Potassium levels should be kept around 5 mmol/l.

During the ion exchange, the resin delivers one sodium ion for each captured potassium ion. Nevertheless, sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. While each gram of resin exchanges about 3 mmol of potassium *in vitro*, it exchanges about 1 mmol *in vivo* (Sweetman, 2012).

Sodium polystyrene sulfonate has been long used in both adults and in children with a good safety profile. However, the oral route is contraindicated in neonates and low- birth-weight infants as they show increased risk of gastrointestinal adverse events (Micromedex, 2012). Long term administration of sodium polystyrene sulfonate may lead to metabolic disorders. Careful biochemical monitoring is needed.

Three published studies reported the adverse events observed in patients receiving the sodium polystyrene sulfonate treatment (Evans et al., 1953; Scheer et al., 1961; Chernin et al., 2012). Chernin et al. conducted a retrospective long-term study evaluating the efficacy and safety of 14 patients with chronic kidney disease, who were treated with sodium polystyrene sulfonate to prevent recurrence of hyperkalaemia, with a median follow-up of 14.5 months. Results indicated that sodium polystyrene sulfonate was well tolerated without severe adverse events attributed directly to its use. Colonic necrosis, a rare complication previously associated with the use of sodium polystyrene sulfonate, was not observed (Chernin et al., 2012).

Regarding safety in preterm infants, subpopulation in which the medicinal product is contraindicated, a recent study conducted by Yaseen et al. indicated that cardiovascular and gastrointestinal events have been reported with the rectal administration of sodium polystyrene sulfonate (Yaseen et al., 2008).

IV.6.2 Common adverse events

The most frequent adverse events are metabolic disorders such as hypocalcaemia; hypokalaemia, that may occur as a consequence of its mechanism of action and gastrointestinal disorders such as nausea and constipation in elderly patients. Nausea may be managed by administration of the resin rectally or by administration of an antiemetic such as

phenothiazine derivative. Constipation may be minimized by the use of a laxative. Concomitant administration of a cathartic to facilitate resin transit through the gastrointestinal tract has also been recommended (Micromedex, 2012). Diarrhoea and anorexia may be occasionally reported.

IV.6.3 Effects on the gastrointestinal tract

Colonic necrosis, including some fatalities, has been reported after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in animals suggested that the use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested as a possible cause. Both colonic and upper gastrointestinal necrosis have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there have also been reports of colonic necrosis with oral or rectal sodium polystyrene sulfonate alone. Sodium polystyrene sulfonate /sorbitol-associated colonic necrosis is most commonly seen in patients who have received enemas in the setting of recent abdominal surgery, bowel injury, or intestinal dysfunction. It is a rare event, on the order of 0.2 to 0.3% cases when considering patients at risk; however, even lower incidence rates of 0.1% are reported in the overall population (Watson et al., 2010). Although the appearance of intestinal necrosis may be a cause of great concern, it should be emphasized that most cases are isolated reports and nearly all related to the concomitant use of sorbitol. Specific warning to avoid this interaction is included in the SmPC.

Another observation that implicated sodium polystyrene sulfonate as the cause of intestinal necrosis was the finding of sodium polystyrene sulfonate crystals in histologic specimens of necrotic bowels of patients. However, this only showed that patients received sodium polystyrene sulfonate because crystals may be seen with a normal bowel or with an unrelated pathology. Crystals are not always seen in the necrotic mucosa of patients reported to have sodium polystyrene sulfonate-induced necrosis. The third type of evidence is of the numerous patients who experienced intestinal necrosis after exposure to sodium polystyrene sulfonate if the patients had no other risk factors for it, such as old age, chronic kidney disease stages IV or V, congestive heart failure, coronary artery disease, diabetes mellitus, peripheral vascular disease, and chronic pulmonary disease. However, these factors were present in most cases of intestinal necrosis ascribed to sodium polystyrene sulfonate. Also, sodium polystyrene sulfonate would appear causative in cases of intestinal necrosis if this complication occurred more often in individuals exposed to sodium polystyrene sulfonate than in those who have not been exposed. It is not clear if sodium polystyrene sulfonate causes intestinal necrosis; instead, it may just be a marker for risk factors for intestinal necrosis, such as chronic and end-stage renal disease. Even if sodium polystyrene sulfonate with or without sorbitol can rarely produce intestinal necrosis, it is so uncommon (much <1%) that physicians should not hesitate to prescribe it for severe hyperkalemia if it might be lifesaving (Abuelo, 2018), (Kim, 2019).

In another retrospective study of 11,409 hemodialysis patients, 20% were prescribed sodium polystyrene sulfonate. Colonic surgery, a marker for colonic necrosis, was no more common in patients who received sodium polystyrene sulfonate (0.6%) than in those not given sodium polystyrene sulfonate (1.0%) (Abuelo,2018).

Pharmacodynamic interactions of sodium polystyrene sulfonate with sorbitol (risk of intestinal necrosis), antacids and laxatives (non-absorbable cation-donating) (risk of metabolic

alkalosis), and cardiac glycosides (risk of potentiation of toxic effects) are known and well described in the SmPC for Sodium Polystyrene Sulfonate 400 g Powder for Suspension (see Modules 2.5 Clinical Overview and 2.7 Clinical Summary for more information). The pharmacodynamic interaction between sodium polystyrene sulfonate and sorbitol has also been described in animals (Lillemoe et a., 1987). Nevertheless, Sodium Polystyrene Sulfonate 400 g Powder for Suspension is a product intended to be used without sorbitol and the proposed SmPC includes a warning to avoid the concomitant administration of Sodium Polystyrene Sulfonate 400 g Powder for Suspension and sorbitol.

Other potential interactions, such as those related with lithium, iron, levothyroxine/thyroxine, are analysed later as pharmacokinetic interactions (see Section 2.4.2.5 Pharmacokinetics Interactions). Therefore, for Sodium Polystyrene Sulfonate 400 g Powder for Suspension no safety concern is recognised or suspected based on the pharmacological class or the clinical experience regarding pharmacodynamic drug interactions if the product is administered according to the SmPC recommendations.

Effects on the gastrointestinal tract include also mild common events such as nausea and constipation (this latter mainly in elderly patients). Very rare or isolated reports of intestinal obstruction, and serpiginous ulcers in the stomach and in the terminal ileum.

IV.6.4 Endocrine/Metabolic Effects

Electrolyte imbalances including hypocalcaemia, hypokalaemia, hypomagnesemia, and significant sodium retention may occur during therapy with sodium polystyrene sulfonate. Close monitoring of electrolytes is recommended (Sweetman, 2012).

Cases of systemic alkalosis have occurred when orally administered cation-exchange resins were used concomitantly with non-absorbable cation-donating antacids and laxatives such as magnesium hydroxide and aluminium carbonate.

IV.6.5 Respiratory effect

Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of three patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in two and with early bronchitis in the third. It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.

IV.6.6 Interactions

The concomitant use of sodium polystyrene sulfonate and sorbitol has been implicated in cases of colonic necrosis, which is a very serious adverse reaction with a potentially fatal outcome. Therefore, the administration of sorbitol should be avoided during treatment with sodium polystyrene sulfonate due to the increased risk for colonic necrosis.

sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, metabolic alkalosis may develop due to binding of the cation by the resin preventing neutralisation of bicarbonate ions

in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient with chronic hypocalcaemia of renal failure given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine, iron and lithium salts. Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

IV.6.7 Precautions

Sodium polystyrene sulfonate should not be given orally to neonates and is contra-indicated by any route in those with reduced gut motility or obstructive bowel disease. Care is also needed with rectal use in neonates and children, as excessive enema dosage or inadequate dilution could result in impaction of the resin. Treatment should be stopped if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis, including fatalities, in patients given this combination (see Effects on the Gastrointestinal Tract) and most licensed product information advises against the use of sorbitol with PSs. Magnesium-containing laxatives are also contra-indicated.

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Gastric irritation, nausea, vomiting constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate, more severe in elderly patients with large doses, and in children if the administration is rectal. Intestinal necrosis and other serious gastrointestinal effects have also occurred. In relation to lungs, particles of sodium polystyrene sulfonate were found at autopsy in the lungs of three patients who had taken the resin orally, associated with acute bronchitis and bronchopneumonia (Sweetman, 2012). It was suggested that the patient should be positioned carefully to avoid aspiration. In fact, Sodium Polystyrene Sulfonate 400 g Powder for Suspension's proposed SmPC includes a warning on the correct use of the product in order to avoid these side effects. Regarding rectal administration of sodium polystyrene sulfonate suspension in sorbitol has been associated rarely with extensive intestinal necrosis in several patients (Mc Evoy, 2012; Ryan, 2012; Sweetman, 2012; Lillemoe et al.,1987). Nevertheless, Sodium Polystyrene Sulfonate 400 g Powder for Suspension does not include sorbitol in its composition and rectal administration is proposed in the SmPC.

IV.7 Risk Management Plan

The 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 Natriumpolystyreensulfonaat Focus.

Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.8 Discussion on the clinical aspects

This national procedure concerns a well-established use application for Natriumpolystyreensulfonaat Focus. For this authorisation, reference is made to the clinical studies and experience with the innovator product Resonium A. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Resonium A, poeder (NAP RVG 08071). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Natriumpolystyreensulfonaat 1 g/g Focus, powder for suspension for oral / rectal use has a proven chemical-pharmaceutical quality. Natriumpolystyreensulfonaat 1 g/g Focus is a well-known medicinal product with an established favourable efficacy and safety profile.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Natriumpolystyreensulfonaat 1 g/g Focus was authorised in the Netherlands on 9 April 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
911912 Type: C.I.3.z	PSUSA: PSUSA/00002472 /202010	SmPC	11-11-2021	Approval	--

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