National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

1. NAME OF THE MEDICINAL PRODUCT

NICHEMER 800 (**Sevelamer Hydrochloride Tablets 800 mg)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Sevelamer Hydrochloride….800 mg

Excipients…….Q.S.

Colour: Titanium Dioxide

List of Excipients:

Sr. No	Ingredients	Specification	Label Claim (mg)	Overages %	mg/Tab	Qty/ Batch (Kg)	Function
SHIFTING/MIXING							
1.	Sevelamer Hydrochloride	IHS	800.00	---	800.00	80.00	Active
2.	Microcrystaline Cellulose (Avicel 102)	BP	---	---	362.00	36.20	Diluent
PASTE PREPARATION							
3.	HYPROMELLOSE	BP			20.00	2.00	Binder
4.	ISO PROPYL ALCOHOL	BP	---	---	250.00	25.00	Solvent
5.	Iso Propyl Alcohol*	BP	---	---	80.00	8.00	Solvent
LUBRICATION							
6.	Colloidal anhydrous silica (Colloidal Silicon Dioxide)	BP	---	---	26.00	2.600	Glidant
7.	Stearic Acid (Powder)	BP	---	---	12.00	1.200	Lubricant
Average Weight of Uncoated Tablets:					**1220.00 mg**	**1220.00 mg ± 5%**	
COATING							
8.	Hypromellose (H.P.M.C. E 15)	BP	---	---	16.00	1.60	Film Forming Agent
9.	Macrogol (PEG 6000)	BP	---	---	4.00	0.40	Plasticizer
10.	Purified Talc	BP	---	---	4.00	0.40	Glidant
11.	Titanium Dioxide	BP	---	---	1.00	0.10	Opacifier
12.	Iso Propyl Alcohol*	BP	---	---	70.00	7.00	Solvent
13.	Dichloromethane* (Methylene Chloride)	BP	---	---	120.00	12.00	
Average Weight of Coated Tablets					**1245.00 mg**	**1245.00 mg ± 5%**	

3. PHARMACEUTICAL FORM

A white coloured caplet shaped film coated tablet having a breakline on one side and other side plain.

Note: The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Sevelamer Hydrochloride is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

Sevelamer Hydrochloride is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus ≥ 1.78 mmol/l.

Sevelamer Hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

4.2 Posology and method ofadministration

Posology

Starting dose

The recommended starting dose of Sevelamer Hydrochloride is 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level. Sevelamer Hydrochloride must be taken three times per day with meals.

Serum phosphorus level in patients	Total daily dose of Sevelamer Hydrochloride to be taken over 3 meals per day
1.78 – 2.42 mmol/l (5.5 – 7.5 mg/dl)	2.4 g*
> 2.42 mmol/l (> 7.5 mg/dl)	4.8 g*

*Plus subsequent titrating, see section "Titration and Maintenance"

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer Hydrochloride should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

Titration and Maintenance

Serum phosphorus levels must be monitored and the dose of Sevelamer Hydrochloride titrated by 0.8 g three times per day (2.4 g/day) increments every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring thereafter.

Patients taking Sevelamer Hydrochloride should adhere to their prescribed diets.

In clinical practice, treatment will be continuous based on the need to control serum phosphorus levels and the daily dose is expected to be an average of approximately 6 g per day.

Special populations

Elderly population

No dosage adjustment is necessary in the elderly population.

Hepatic impairment

No studies have been performed in patients with hepatic impairment.

Paediatric population

The safety and efficacy of Sevelamer Hydrochloride in children below the age of 6 years or in children with a BSA below 0.75 m2 have not been established. No data are available.

The safety and efficacy of Sevelamer Hydrochloride in children over 6 years of age and a BSA > 0.75 m2 have been established. Current available data are described in section 5.1.

For paediatric patients, oral suspensions suitable for paediatric use which may be available, should

be administered, as tablet formulations are not appropriate for this population

Method of administration

For oral use.

Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Sevelamer Hydrochloride should be taken with food and not on an empty stomach

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypophosphataemia
- Bowel obstruction

4.4 Special warnings and precautions for use

The safety and efficacy of Sevelamer Hydrochloride have not been established in adult patients with chronic kidney disease not on dialysis with serum phosphorus < 1.78 mmol/l. Therefore it is currently not recommended for use in these patients.

The safety and efficacy of Sevelamer Hydrochloride have not been established in patients with the following disorders:

• dysphagia

• swallowing disorders

• severe gastrointestinal motility disorders including untreated or severe gastroparesis, retention of gastric contents and abnormal or irregular bowel motion

• active inflammatory bowel disease

• major gastrointestinal tract surgery

Treatment of these patients with Sevelamer Hydrochloride should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Sevelamer Hydrochloride treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Intestinal obstruction and ileus/subileus

In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride capsules/tablets, which contain the same active moiety as Sevelamer Hydrochloride. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Sevelamer Hydrochloride. Sevelamer Hydrochloride treatment should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Fat-soluble vitamins and folate deficiency

Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, depending on dietary intake and the severity of their disease. It cannot be excluded that Sevelamer Hydrochloride can bind fat-soluble vitamins contained in ingested food. In patients not taking supplemental vitamins but on

sevelamer, serum vitamin A, D, E and K status should be assessed regularly. It is recommended that vitamin supplements be given if necessary. It is recommended that CKD patients not on dialysis are given vitamin D supplements (approximately 400 IU of native vitamin D daily) which can be part of a multivitamin preparation to be taken apart from their dose of Sevelamer Hydrochloride. In patients undergoing peritoneal dialysis additional monitoring of fat soluble vitamins and folic acid is recommended, since vitamin A, D, E and K levels were not measured in a clinical study in these patients.

There is at present insufficient data to exclude the possibility of folate deficiency during long term Sevelamer Hydrochloride treatment. In patients not taking supplemental folic acid but on sevelamer, folate level should be assessed regularly.

Hypocalcaemia/hypercalcaemia

Patients with CKD may develop hypocalcaemia or hypercalcaemia. Sevelamer Hydrochloride does not contain any calcium. Serum calcium levels should therefore be monitored at regular intervals and elemental calcium should be given as a supplement if required.

Metabolic acidosis

Patients with CKD are predisposed to developing metabolic acidosis. As part of good clinical practice, monitoring of serum bicarbonate levels is therefore recommended.

Peritonitis

Patients receiving dialysis are subject to certain risks for infection specific to dialysis modality. Peritonitis is a known complication in patients receiving peritoneal dialysis and in a clinical trial with sevelamer hydrochloride, a greater number of peritonitis cases were reported in the sevelamer group than in the control group. Patients on peritoneal dialysis should be closely monitored to ensure the correct use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Swallowing and choking difficulties

Uncommon reports of difficulty swallowing the Sevelamer Hydrochloride tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. Proper swallowing ability should be carefully monitored in patients with co-morbid conditions. The use of Sevelamer Hydrochloride powder in patients with a history of difficulty swallowing should be considered.

Hypothyroidism

Closer monitoring of patients with hypothyroidism co-administered with Sevelamer Hydrochloride and levothyroxine is recommended.

Hyperparathyroidism

Sevelamer Hydrochloride is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism, Sevelamer Hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25 – dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels.

Inflammatory gastrointestinal disorders

Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as bleeding, perforation, ulceration, necrosis, colitis) associated with the presence of sevelamer crystals have been reported in literature. However, the causality of the sevelamer crystals in initiating such disorders has not been demonstrated. Sevelamer Hydrochloride treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

Excipients Sevelamer Hydrochloride tablets contain lactose. Patients with rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of interaction

Dialysis

Interaction studies have not been conducted in patients on dialysis.

Ciprofloxacin

In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Sevelamer Hydrochloride, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, Sevelamer Hydrochloride should not be taken simultaneously with ciprofloxacin.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients

Reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when co-administered with sevelamer hydrochloride without any clinical consequences (e.g., graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of ciclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

Levothyroxine

Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer hydrochloride, which contains the same active moiety as Sevelamer Hydrochloride, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving Sevelamer Hydrochloride and levothyroxine.

Anti-arrhythmics and anti-seizure medicinal products

Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti- seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Therefore, possible reduction in absorption cannot be excluded. The anti-arrhythmic medicinal product should be taken at least one hour before or three hours after Sevelamer Hydrochloride, and blood monitoring can be considered.

Digoxin, warfarin, enalapril or metoprolol

In interaction studies in healthy volunteers, sevelamer hydrochloride, which contains the same active moiety as Sevelamer Hydrochloride, had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol.

Proton pump inhibitors

During post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with Sevelamer Hydrochloride. Caution should be exercised when prescribing PPI to patients concomitantly treated with Sevelamer Hydrochloride. The phosphate serum level should be monitored and the Sevelamer Hydrochloride dosage adjusted consequently.

Bioavailability

Sevelamer Hydrochloride is not absorbed and may affect the bioavailability of other medicinal products. When administering any medicinal product where a reduction in the bioavailability could have a clinically significant effect on safety or efficacy, the medicinal product should be administered at least one hour before or three hours after Sevelamer Hydrochloride, or the physician should consider monitoring blood levels

4.6 Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of sevelamer in pregnant women. Animal studies have shown some reproductive toxicity when sevelamer was administered to rats at high doses. Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid. The potential risk to humans is unknown. Sevelamer Hydrochloride should only be given to pregnant women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the foetus.

Breast-feeding

It is unknown whether sevelamer/metabolites are excreted in human milk. The non-absorbed nature of sevelamer indicates that excretion of sevelamer in breast milk is unlikely. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Sevelamer Hydrochloride should be made taking into account the benefit of breast-feeding to the child and the benefit of Sevelamer Hydrochloride therapy to the woman.

Fertility

There are no data from the effect of sevelamer on fertility in humans. Studies in animals have shown that sevelamer did not impair fertility in male or female rats at exposures at a human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative BSA

4.7 Effects on ability to drive and use machines

Sevelamer has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring (≥ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild to moderate in intensity.

Tabulated list of adverse reactions

The safety of sevelamer (as either carbonate and hydrochloride salts) has been investigated in numerous clinical trials involving a total of 969 haemodialysis patients with treatment duration of 4 to 50 weeks (724 patients treated with sevelamer hydrochloride and 245 with Sevelamer Hydrochloride), 97 peritoneal dialysis patients with treatment duration of 12 weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8 to 12 weeks (79 patients treatment with sevelamer hydrochloride and 49 with Sevelamer Hydrochloride).

Adverse reactions that occurred during clinical trials or that were spontaneously reported from post-marketing are listed by frequency in the table below. The reporting rate is classified as very common (≥1/10), common (≥1/100to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Very common	Common	Very rare	Not known
Immune system disorders		Hypersensitivity*		
Gastrointestinal disorders	Nausea, vomiting, upper abdominal pain, constipation	Diarrhoea, dyspepsia, flatulence, abdominal pain	Intestinal obstruction, ileus/subileus, intestinal perforation	
Skin and subcutaneous tissue disorders			Pruritus, rash	

* post-marketing experience

Paediatric population

In general, the safety profile for children and adolescents (6 to 18 years of age) is similar to the safety profile for adults.

4.9 Overdose

Sevelamer hydrochloride, which contains the same active moiety as Sevelamer Hydrochloride, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse reactions. In CKD patients, the maximum average daily dose studied was 14.4 grams of Sevelamer Hydrochloride in a single daily dose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties

Pharmacotherapeutic group: Treatment of hyperkalaemia and hyperphosphataemia.

ATC code: V03A E02.

Mechanism of action

Sevelamer Hydrochloride contains sevelamer, a non-absorbed phosphate binding crosslinked polymer, free of metal and calcium. Sevelamer contains multiple amines separated by one carbon from the polymer backbone which become protonated in the stomach. These protonated amines bind negatively charged ions such as dietary phosphate in the intestine.

Pharmacodynamic effect

By binding phosphate in the gastrointestinal tract and decreasing absorption, sevelamer lowersthe phosphorus concentration in the serum. Regular monitoring of serum phosphorus levels is always necessary during phosphate binder administration.

Clinical efficacy and safety

In two randomised, cross over clinical trials, Sevelamer Hydrochloride in both tablet and powder formulations when administered three times per day has been shown to be therapeutically equivalent to sevelamer hydrochloride and therefore effective in controlling serumphosphorus in CKD patients on haemodialysis.

The first study demonstrated that Sevelamer Hydrochloride tablets dosed three times per day was equivalent to sevelamer hydrochloride tablets dosed three times per day in 79 haemodialysis patients treated over two randomised 8 week treatment periods (mean serum phosphorus time-weighted averages were 1.5 ± 0.3 mmol/l for both Sevelamer Hydrochloride and sevelamer hydrochloride). The second study demonstrated that Sevelamer Hydrochloride powder dosed three times per day was equivalent to sevelamer hydrochloride tablets dosed three times per day in 31 hyperphosphataemic (defined as serum phosphorus levels ≥ 1.78 mmol/l) haemodialysis patients over two randomised 4 week treatment periods (mean serum phosphorus time weighted averages were 1.6 ± 0.5 mmol/l for Sevelamer Hydrochloride powder and 1.7 ± 0.4 mmol/l for sevelamer hydrochloride tablets).

In the clinical trials in haemodialysis patients, sevelamer alone did not have a consistent and clinically significant effect on serum intact parathyroid hormone (iPTH). In a 12 week study involving peritoneal dialysis patients however, similar iPTH reductions were seen compared with patients receiving calcium acetate. In patients with secondary hyperparathyroidism, Sevelamer Hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium as supplements, 1,25 – dihydroxy Vitamin D3 or one of its analogues to lower the (iPTH) levels.

Sevelamer has been shown to bind bile acids in vitro and in vivo in experimental animal models. Bile acid binding by ion exchange resins is a well-established method of lowering blood cholesterol. In clinical trials of sevelamer, both the mean total-cholesterol and LDL- cholesterol declined by 15-

39%. The decrease in cholesterol has been observed after 2 weeks of treatment and is maintained with long-term treatment. Triglycerides, HDL-cholesterol and albumin levels did not change following sevelamer treatment.

Because sevelamer binds bile acids, it may interfere with the absorption of fat soluble vitamins such as A, D, E and K.

Sevelamer does not contain calcium and decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone. The effects of sevelamer on phosphorus and calcium were proven to be maintained throughout a study with one year follow-up. This information was obtained from studies in which sevelamer hydrochloride was used.

Paediatric population

The safety and effectiveness of Sevelamer Hydrochloride in hyperphosphatemic paediatric patients with (CKD) was evaluated in a multicentre study with a 2-week, randomized, placebo-controlled, Fixed Dose Period (FDP) followed by a 6-month, single-arm, open-label, Dose Titration Period (DTP). A total of 101 patients (6 to 18 years old with a BSA range of 0.8 m2 to 2.4 m2) were randomized in the study. Forty-nine (49) patients received Sevelamer Hydrochloride and 51 received placebo during the 2-week FDP. Thereafter all patients received Sevelamer Hydrochloride for the 26-week DTP. The study met its primary endpoint, meaning Sevelamer Hydrochloride reduced serum phosphorus by an LS mean difference of -0.90 mg/dL compared to placebo, and secondary efficacy endpoints. In paediatric patients with hyperphosphatemia secondary to CKD, Sevelamer Hydrochloride significantly reduced serum phosphorus levels compared to placebo during a 2-week FDP. The treatment response was maintained in the paediatric patients who received Sevelamer Hydrochloride during the 6-month open-label DTP. 27% of paediatric patients reached their age appropriate serum phosphorus level at end of treatment. These figures were 23% and 15% in the subgroup of patients on hemodialysis and peritoneal dialysis, respectively. The treatment response during the 2-week FDP was not affected by (BSA), in contrast however, no treatment response was observed in pediatric patients with qualifying phosphorus levels <7.0 mg/dL. Most of adverse events reported as related or possibly related to Sevelamer Hydrochloride were gastrointestinal in nature. No new risks or safety signals were identified with the use of Sevelamer Hydrochloride during the study.

5.2 Preclinical safety data

Pharmacokinetic studies have not been carried out with Sevelamer Hydrochloride. Sevelamer hydrochloride, which contains the same active moiety as Sevelamer Hydrochloride, is not absorbed from the gastrointestinal tract, as confirmed by an absorption study in healthy volunteers.

In a clinical trial of one year, no evidence of accumulation of sevelamer was seen. However, the potential absorption and accumulation of sevelamer during long-term chronic treatment (> one year) cannot be totally excluded.

5.3 Preclinical safety data

Non-clinical data with sevelamer reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Carcinogenicity studies with oral sevelamer hydrochloride were conducted in mice (doses of up to 9 g/kg/day) and rats (0.3, 1, or 3 g/kg/day). There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 14.4 g). There was no increased incidence of tumors observed in mice (human equivalent dose 3 times the maximum clinical trial dose).

In an in vitro mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

In rats and dogs, sevelamer reduced absorption of fat soluble vitamins D, E and K (coagulation factors), and folic acid.

Deficits in skeletal ossification were observed in several locations in foetuses of female rats dosed with sevelamer at intermediate and high doses (human equivalent dose less than the maximum clinical trial dose of 14.4 g). The effects may be secondary to vitamin D depletion.

In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 2 times the maximum clinical trial dose of 13 g/day, based on a comparison of relative BSA).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystaline Cellulose (Avicel 102)
Povidone (PVPK30)
Colloidal Anhydrous silica
HYPROMELLOSE BP
Stearic acid
Hypromellose (H.P.M.C.E 15)
Macrogol (PEG 6000)
Purified talc
Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Store in a Cool Dry Place. Protect From Light.

6.5 Nature and contents of container

10 Tablets packed in one Alu-Alu Blister. Such 3 Alu-Alu Blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

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