SUMMARY OF PRODUCT CHARACTERISTICS

Foseal-800

(Sevelamer Hydrochloride Tablets 800 mg)

TABLE OF CONTENTS

1. NAME OF THE MEDICINAL PRODUCT 3
2. QUALITATIVE AND QUANTITATIVE COMPOSITION 3
3. PHARMACEUTICAL FORM 3
4. CLINICAL PARTICULARS 3
4.1 Therapeutic indications 3
4.2 Posology and method of administration 3
4.3 Contraindications 3
4.4 Special warnings and special precautions for use 5
4.5 Interaction with other medicinal products and other forms of Interaction 6
4.6 Pregnancy and lactation 8
4.7 Effects on ability to drive and use machines 8
4.8 Undesirable effects 9
4.9 Overdose 9
5. PHARMACOLOGICAL PROPERTIES 10
5.1 Pharmacodynamic properties 10
5.2 Pharmacokinetic properties 10
5.3 Preclinical safety data 11
6. PHARMACEUTICAL PARTICULARS 11
6.1 List of excipients 11
6.2 Incompatibilities 11
6.3 Shelf life 11
6.4 Special precautions for storage 11
6.5 Nature and contents of container 11
6.6 Special Precautions for Disposal and Other handling..... 12
7. MARKETING AUTHORISATION HOLDER 13
8. MARKETING AUTHORISATION NUMBER(S) 13
9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION 13
10. DATE OF REVISION OF THE TEXT 13

1. NAME OF THE MEDICINAL PRODUCT

Foseal -800

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Sevelamer Hydrochloride 800 mg

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Foseal is indicated for the control of serum phosphorus in patients with Chronic Kidney Disease (CKD) on hemodialysis. The safety and efficacy of sevelamer in patients who are not on hemodialysis have not been studied. In hemodialysis patients, sevelamer decreases the incidence of hypercalcemic episodes relative to patients on calcium treatment.

4.2 Posology and method of administration

Children: The safety and efficacy of this product has not been established in patients below the age of 18 years.

Adult patients Not Taking a Phosphate Binder: The recommended starting dose of sevelamer is 800 to 1600 mg, which can be administered as one to two 800 mg Tablets or two to four 400 mg Tablets with each meal based on serum phosphorus level. Table 1 provides recommended starting doses of Sevelamer for patients not taking a phosphate binder.

Table 1: Starting Dose for Patients Not Taking a Phosphate Binder

Serum Phosphorus	Sevelamer 800 mg Tablet	Sevelamer 400 mg Tablet
>5.5 and < 7.5 mg/dl	1 tablet three times daily with meals	2 tablets three times daily with meals
≥ 7.5 and <9 mg/dl	2 tablets three times daily with meals	3 tablets three times daily with meals
≥ 9 mg/dl	2 tablets three times daily with meals	4 tablets three times daily with meals

Patients Switching From Calcium Acetate: Table 2 gives recommended starting doses of sevelamer based on a patient's current calcium acetate dose.

Table 2: Starting Dose for Patients Switching From Calcium Acetate to Sevelamer

Calcium acetate 667 mg (Tablets per meal)	Sevelamer 800 mg (Tablets per meal)	Sevelamer 400 mg (Tablets per meal)
1 tablet	1 tablet	2 tablets
2 tablets	2 tablets	3 tablets
3 tablets	3 tablets	5 tablets

Dose Titration for All Patients Taking Sevelamer: Dosage should be adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to 5.5 mg/dL or less. The dose may be increased or decreased by one tablet per meal at two-week intervals as necessary. Table 3 gives a dose titration guideline.

Table 3: Dose Titration Guideline

Serum Phosphorus	Sevelamer dose
> 5.5 mg/dl	Increase 1 tablet per meal at 2 week intervals
3.5–5.5 mg/dl	Maintain current dose
< 3.5 mg/dl	Decrease 1 tablet per meal

4.3 Contraindications

- Hypophosphataemia or bowel obstruction.
- Hypersensitivity to sevelamer or to any of the ingredients of the product

4.4 Special warnings and special precautions for use

Efficacy and safety of sevelamer has not been studied in children, in predialysis patients or in patients receiving peritoneal dialysis treatment.

The safety and efficacy of sevelamer has not been studied in patients with swallowing disorders, untreated or severe gastroparesis, and retention of gastric contents. Foseal should only be used in these patients following careful assessment of benefit and risks.

Efficacy and safety of sevelamer has not been studied in patients with active inflammatory bowel disease, gastrointestinal motility disorders, abnormal or irregular bowel motion and patients with a history of major gastrointestinal surgery. Consequently, caution should be exercised when Foseal is used in patients with these disorders.

In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with Foseal. Foseal treatment should be re-evaluated in patients who develop severe constipation.

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

Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. Foseal does not contain calcium. Serum calcium levels should be monitored as is done in normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Depending on diet intake and the nature of end stage renal failure, dialysis patients may develop low vitamin A, D, E and K levels. Therefore, in patients not taking these vitamins, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of thromboplastin time should be considered and the vitamins should be supplemented if necessary.

There is at present insufficient data to exclude the possibility of folate deficiency during long term sevelamer treatment.

Serum chloride may increase during sevelamer treatment as chloride may be exchanged for phosphorus in the intestinal lumen. Although no clinically significant serum chloride increase has been observed in the clinical studies, serum chloride should be monitored as is done in the routine follow-up of a dialysis patient.

Patients with chronic renal failure are predisposed to developing metabolic acidosis. Worsening of acidosis has been reported upon switching from other phosphate binders to sevelamer in a number of studies where lower bicarbonate levels in the sevelamer-treated patients compared to patients treated with calcium-based binders were observed. Closer monitoring of serum bicarbonate levels is therefore recommended.

Very rare cases of hypothyroidism have been reported in patients co-administered sevelamer and Levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both drugs.

As data on the chronic use of sevelamer for over one year are not yet available, potential absorption and accumulation of sevelamer during long-term chronic treatment cannot be totally excluded (see section 5.2 Pharmacokinetics).

4.5 Interaction with other medicinal products and other forms of Interaction

Interaction studies have not been conducted in patients on haemodialysis.

In interaction studies in healthy volunteers, sevelamer had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer in a single dose study. Consequently, sevelamer should not be taken simultaneously with ciprofloxacin.

Sevelamer may affect the bioavailability of other medicinal products. Reduced levels of cyclosporine and mycophenolate mofetil have been reported in transplant patients when coadministered with sevelamer without any clinical consequences (i.e graft rejection). The possibility of an interaction cannot be excluded and a close monitoring of blood concentrations of mycophenolate mofetil and cyclosporine should be considered during the use of combination and after its withdrawal. 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, or the physician should consider monitoring blood levels.

In animal studies, co-administration of a single dose of sevelamer with verapamil, quinidine, calcitriol, tetracycline, warfarin, valproic acid, digoxin, propranolol, estrone and L-thyroxin did not alter peak serum concentrations or area under the curve for serum concentrations of these products.

4.6 Pregnancy and lactation

The safety of sevelamer has not been established in pregnant or lactating women. In animal studies there was no evidence that sevelamer induced embryo-foetal toxicity. Sevelamer should only be given to pregnant or lactating women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the foetus or infant (See 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

In a parallel design study involving 202 patients with treatment duration of 52 weeks, the most frequently occurring (5% of patients) undesirable effects possibly or probably related to sevelamer were all in the gastrointestinal disorders system organ class. Data possibly or probably related to sevelamer from this study and from uncontrolled clinical trials involving 384 patients are listed by frequency in the table below. The reporting rate is classified as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

Gastrointestinal Disorders
Very common : Nausea, vomiting, abdominal pain, constipation, diarrhoea, dyspepsia
Common : Flatulence
Nervous system disorders
Very common: Headache
Vascular disorders
Very common : Hypotension, hypertension
General disorders and administration site conditions
Very common : Pain
Skin and subcutaneous disorders
Very common : Pruritis
Common: Rash
Infections and infestations
Common : Pharyngitis

Most of these events are commonly observed in patients Stage 5 Chronic Kidney Disease and are not necessarily attributable to sevelamer. Post-marketing experience: In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer.

4.9 Overdose

No case of overdose has been reported. Sevelamer has been given to normal healthy volunteers in doses up to 14 grams, the equivalent of thirty-five 403 mg capsules (equivalent to seventeen 800 mg tablets), per day for eight days with no undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Foseal contains sevelamer, a non-absorbed phosphate binding poly (allylamine hydrochloride) polymer, free of metal and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the dietary tract, sevelamer lowers the phosphate concentration in the serum. Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium based phosphate binders alone, probably because the product itself does not contain calcium. The effects on phosphate and calcium were proven to be maintained throughout a study with one year follow-up. 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 mean total and LDL cholesterol declined by 15-31%. This effect is observed after 2 weeks is maintained with long-term treatment. Triglycerides, HDL cholesterol and albumin did not change. In the clinical studies in haemodialysis patients, sevelamer alone did not have a consistent and clinically significant effect on serum intact parathyroid hormone (iPTH). In patients with secondary hyperparathyroidism sevelamer should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25 – dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (iPTH) levels. No data are available on the effect of sevelamer treatment on bone.

5.2 Pharmacokinetic properties

Sevelamer is not absorbed from the gastrointestinal tract according to a single dose pharmacokinetic study in healthy volunteers. Pharmacokinetic studies have not been carried out in renal failure patients (see section 4.4 Special warnings and special precautions for use).

5.3 Preclinical safety data

In preclinical studies in rats and dogs, sevelamer at a dose of 10 times the maximum human doses reduced absorption of fat soluble vitamins D, E and K, and folic acid. In a study in rats, administering sevelamer in 15-30 x the human dose, an increase in serum copper was detected. This was not confirmed in a dog study or in clinical trials. Currently, no formal carcinogenicity data are available. However, in vitro and in vivo studies have indicated that sevelamer does not have genotoxic potential. Also the medicinal product is not absorbed in the gastrointestinal tract. In reproduction studies there was no evidence that sevelamer induced embryolethality, foetotoxicity or teratogenicity at the doses tested (up to 1 g/kg/day in rabbits and up to 4.5 g/kg/day in rats). Deficits in skeletal ossification were observed in several locations in fetuses of female rats dosed with sevelamer at 8-20 times the maximum human dose of 200 mg/kg. The effects may be secondary to vitamin D and/or vitamin K depletion at these high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn Starch
Povidone
Colloidal Silicon Dioxide
Stearic Acid
Hypromellose
Isopropyl Alcohol
Methylene Chloride
Talc
Macrogols

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active Ingredients.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30ºC. Protect from light.

6.5 Nature and contents of container

10 Tablets are packed in an Alu-Alu blister. 1 such Alu-Alu blisters is packed in an overprinted carton bearing all batch details along with a pack insert.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

21st November, 2020.