SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

LAMSEV 800

Sevelamer Carbonate Tablets 800 mg

Pharmaceutical dosage form

Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSTIONS

Sevelamer Carbonate Tablets 800 mg:

Each film-coated tablet contains 800 mg of Sevelamer carbonate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sevelamer Carbonate Tablets 800 mg:

White to off white, oval shaped, film-coated tablets, imprinted with “J 75” on one side withEdible Black ink and plain on other side.

4. CLINICAL PARTICULARS

4.1.Therapeutic indications

Sevelamer is indicated for the control of hyperphosphataemia in adult patients receivinghaemodialysis or peritoneal dialysis.

Sevelamer is also indicated for the control of hyperphosphataemia in adult patients with chronic

kidney disease not on dialysis with serum phosphorus $\geq$ 1.78 mmol/l.

Sevelamer should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1, 25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.

4.2.Posology and method of administration

Posology

Starting dose

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

Serum phosphorus level in patients	Total daily dose of sevelamer carbonate to be taken over 3meals 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 as per instructions

For patients previously on phosphate binders (sevelamer hydrochloride or calcium based), Sevelamer 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 carbonate titrated by

0.8 g three times per day(2.4 g/day) increment every 2-4 weeks until an acceptable serumphosphorus level is reached, with regular monitoring thereafter.

Patients taking Sevelamer should adhere to their prescribed diets.

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

Paediatric population

The safety and efficacy of Sevelamer has not been established in children below the age of 18years.

Sevelamer is not recommended in children below the age of 18 years.

Method of administration

For oral use.

Tablets should be swallowed intact and should not be crushed, chewed, or broken into piecesprior to administration.

3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Hypophosphataemia

- Bowel obstruction.

4. Special warnings and precautions for use

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

The safety and efficacy of Sevelamer have not been established in patients with the followingdisorders:

- 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

Therefore, caution should be exercised when Sevelamer is used in these patients.

Intestinal obstruction and ileus/subileus

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

Fat-soluble vitamins

Patients with CKD may develop low levels of fat-soluble vitamins A, D, E and K, dependingon dietary intake and the severity of their disease. It cannot be excluded that Sevelamer 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. 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 notmeasured in a clinical study in these patients.

Folate deficiency

There is at present insufficient data to exclude the possibility of folate deficiency during longterm Sevelamer treatment.

Hypocalcaemia/hypercalcaemia

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

Metabolic acidosis

Patients with chronic kidney disease are predisposed to developing metabolic acidosis. As partof 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 study 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 tablet have been reported. Many of these cases involved patients with co-morbid conditions including swallowing disorders or oesophageal abnormalities. Caution should be exercised when Sevelamer is used in patients with difficulty swallowing. For patients with swallowing difficulties, sevelamer carbonate isalso available as a powder for oral suspension.

Hypothyroidism

Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonateand levothyroxine is recommended (see section 4.5).

Long-term chronic treatment

In a clinical trial of one yeaar, 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 (see section 5.2).

Hyperparathyroidism

Sevelamer is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism Sevelamer 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 carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

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 in Sevelamer, decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, Sevelamer 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 (i.e 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 carbonate, and levothyroxine. Closer monitoring of thyroid stimulating hormone (TSH) levels is therefore recommended in patients receiving sevelamer carbonate 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. Caution should be exercised when prescribing Sevelamer to patients also taking thesemedicinal products

Digoxin, warfarin, enalapril or metoprolol

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

Proton pump inhibitors

During post-marketing experience, very rare cases of increased phosphate levels have beenreported in patients taking proton pump inhibitors co-administered with sevelamer carbonate.

Bioavailability

Sevelamer 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, or the physician should considermonitoring blood levels.

6. Fertility, 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 (see section 5.3). Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid (see sections 4.4 and 5.3). The potential risk to humans is unknown. Sevelamer 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 should be made taking into account the benefit of breast-feeding to the child andthe benefit of Sevelamer therapy to the woman.

Fertility

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

7. Effects on ability to drive and use machines

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

8. Undesirable effects

Summary of the safety profile

The most frequently occurring ($\geq$ 5% of patients) adverse reactions were all in the gastrointestinal disorders system organ class. Most of these adverse reactions were mild tomoderate 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 carbonate), 97 peritoneal dialysis patients with treatment duration of 12weeks (all treated with sevelamer hydrochloride) and 128 patients with CKD not on dialysis with treatment duration of 8to 12 weeks (79 patients treatment with sevelamer hydrochloride and 49 with sevelamercarbonate).

Adverse reactions that occurred during clinical studies or that were spontaneously reported from post marketing experience are listed by frequency in the table below. The reporting rate

is classified as very common (≥1/10), common (≥1/100 to <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 OrganClass	**Very Common**	**Common**	**Very rare**	**Not known**
Immune system disorders			Hypersensitivity*	
Gastrointestinaldisorders	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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1.Pharmacodynamic properties

Pharmacotherapeutic group: Treatment of hyperkalaemia and hyperphosphataemia.ATC code: V03A E02.

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

In two randomised, cross over clinical studies, sevelamer carbonate 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 serum phosphorus in CKD patients on haemodialysis.

The first study demonstrated that sevelamer carbonate 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 carbonate and sevelamer hydrochloride). The second study demonstrated that sevelamer carbonate powder dosed three times per day was equivalent to sevelamer hydrochloride tablets dosed three times per day in

patients over two randomised 4 week treatment periods (mean serum phosphorus 31 hyperphosphataemic (defined as serum phosphorus levels $\geq$ 1.78 mmol/l) haemodialysis time- weighted averages were 1.6 ± 0.5 mmol/l for sevelamer carbonate powder and 1.7 ± 0.4 mmol/l for sevelamer hydrochloride tablets).

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 a 12 week study involving peritoneal dialysis patients however, similar iPTH reductions were seen comparedwith patients receiving calcium acetate. In patients with secondary hyperparathyroidism Sevelamer should be used within the context of a multiple therapeutic approach, which could

include calcium as supplements, 1, 25 – dihydroxy Vitamin D_3 or one of its analogues to lower the intact parathyroid hormone (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 hypercalcemic 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.

5.2. Pharmacokinetic properties

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

5.3. Preclinical safety data

Non-clinical data with sevelamer reveal no special hazard for humans based on conventionalstudies 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 ratsdosed 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 body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1.List of excipients

Mannitol, Crospovidone, Hydroxypropyl Cellulose, Colloidal silicon dioxide, Talc, GlycerylBehenate.

Coating Material:

Aquarius Prime BBN119000 clear
containsHypromellose 2910,
HPMC.003A Hypromellose 2910 and
Acetylated Monoglyceride FCC/ E472a

Opacode Black S-1-17823 contains
Shellac Glaze -45% (20% Esterified) In Ethanol,
Isopropyl Alcohol,
Iron Oxide Black,
N- Butyl Alcohol,
Propylene Glycol and
Ammonium Hydroxide 28 %

6.2. Incompatibilities

Not applicable.

6.3.Shelf life

24 Months

6.4.Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

HDPE Bottle with a polypropylene cap containing 30 Tablets.

6.6.Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER:

Manufacturer:

AUROBINDO PHARMA LTD., Unit VII,
SEZ, TSIIC, Plot No. S1, Survey No's:
411/P, 425/P, 434/P, 435/P & 458/P,
Green Industrial Park, Polepally village,
Jedcherla Mandal, Mahaboobnagar
District,Telangana, India.

Marketing Authorization Holder:
Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar, Ameerpet,
Hyderabad-500 038,Telangana
State, India.

8. MARKETING AUTHORIZATION NUMBER(S):

TAN 22 HM 0436

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

07th October, 2022

10. DATE OF REVISION OF THE TEXT

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