Velsone
Sevelamer Carbonate

1. NAME OF THE MEDICINAL PRODUCT
Velsone 800mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 800mg of Sevelamer Carbonate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film Coated Tablets.
Off white, oval shaped film-coated tablet, debossed with 'C 22' on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Velsone is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

Velsone 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.

Velsone 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
Because of the rapid disintegration of the carbonate salt tablet and its rapid reaction with the hydrochloric acid in the stomach, the dosing of Velsone is anticipated to be similar to that of the hydrochloride salt.

Velsone should be given three times a day with meals.

Patients Not Taking a Phosphate Binder. The recommended starting dose of Velsone is 800 to 1600 mg, which can be administered as one or two Velsone 800 mg tablets, with meals based on serum phosphorus level. Table 1 provides recommended starting doses of Velsone for patients not taking a phosphate binder.

TABLE 1. STARTING DOSE FOR PATIENTS NOT TAKING A PHOSPHATE BINDER

Serum Phosphorus	Velsone
> 1.78 and < 2.42 mmol/L	1 tablet three times daily with meals
> 2.42 and < 2.91 mmol/L	2 tablets three times daily with meals
> 2.91 mmol/L	2 tablets three times daily with meals

Patients Switching From Sevelamer Hydrochloride. For patients switching from sevelamer hydrochloride, sevelamer carbonate should be prescribed on a gram per gram basis. Further titration to the desired phosphate levels may be necessary. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Patients Switching From Calcium Acetate. In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of Velsone based on a patient's current calcium acetate dose.

TABLE 2. STARTING DOSE FOR DIALYSIS PATIENTS SWITCHING FROM CALCIUM ACETATE TO VELSONE

Calcium Acetate 667 mg (Tablets per meal)	Velsone (Tablets per meal)
1 tablet	1 tablet
2 tablets	2 tablets
3 tablets	3 tablets

Dose Titration for All Patients Taking Velsone. The dose should be increased or decreased by one tablet per meal at two week intervals, as necessary, with the goal of controlling serum phosphorus within the target range of 1.13 mmol/L to 1.78 mmol/L.

Method of administration
Oral use
Tablets should be swallowed intact and should not be crushed, chewed, or broken into pieces prior to administration. Velsone 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 carbonate 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 carbonate 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 Velsone should only be initiated after careful benefit/risk assessment. If the therapy is initiated, patients suffering from these disorders should be monitored. Velsone 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 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 Velsone. The 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 carbonate 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 carbonate. 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 carbonate 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 carbonate 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 Velsone 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 carbonate powder in patients with a history of difficulty swallowing should be considered.

Hypothyroidism
Closer monitoring of patients with hypothyroidism co-administered with sevelamer carbonate and levothyroxine is recommended.

Hyperparathyroidism
Sevelamer carbonate is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism, sevelamer carbonate 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.

Inflammatory gastrointestinal disorders
Cases of serious inflammatory disorders of different parts of the gastrointestinal tract (including serious complications such as haemorrhage, perforation, ulceration, necrosis, colitis and colonic/caecal mass) associated with the presence of sevelamer crystals have been reported. Inflammatory disorders may resolve upon sevelamer discontinuation. Sevelamer carbonate treatment should be re-evaluated in patients who develop severe gastrointestinal symptoms.

4.5. Interactions with other medicinal products and other forms of interaction
There are no empirical data on avoiding drug interactions between Sevelamer Carbonate and most concomitant oral drugs. For oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy (e.g., cyclosporine, tacrolimus, levothyroxine), consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended-release product. Where possible consider monitoring clinical responses and/or blood levels of concomitant drugs that have a narrow therapeutic range.

TABLE 3. SEVELAMER DRUG INTERACTIONS

Oral drugs for which sevelamer did not alter the pharmacokinetics when administered concomitantly	
Digoxin Enalapril Iron Metoprolol Warfarin	
Oral drugs that have demonstrated interaction with sevelamer and are to be dosed separately from Sevelamer Carbonate	
Ciprofloxacin	**Dosing Recommendations** Take at least 2 hours before or 6 hours after sevelamer
Mycophenolate mofetil	Take at least 2 hours before sevelamer

Cyclosporin, mycophenolate mofetil and tacrolimus in transplant patients
Reduced levels of cyclosporin, 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 cyclosporin, mycophenolate mofetil and tacrolimus should be considered during the use of combination and after its withdrawal.

4.6. Fertility, pregnancy and lactation
Pregnancy
There are no or limited amount of data from the use of sevelamer in pregnant women. Sevelamer has also been shown to reduce the absorption of several vitamins including folic acid. The potential risk to humans is unknown.

Sevelamer carbonate 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 carbonate should be made taking into account the benefit of breast-feeding to the child and the benefit of sevelamer carbonate therapy to the woman.

Fertility
There are no data from the effect of sevelamer on fertility in humans.

4.7. Effects on ability to drive and use machine
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 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
Adverse reactions that occurred are listed by frequency in the table below. The reporting rate is classified as very common, common, uncommon, rare, very rare, not known.

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[1], gastrointestinal haemorrhage*[1], intestinal ulceration*[1], gastrointestinal necrosis*[1], colitis*[1], intestinal mass*[1]
Skin and subcutaneous tissue disorders				Pruritus, rash
Investigations				Crystal deposit intestine*[1]

*post-marketing experience
[1]See inflammatory gastrointestinal disorders warning in section Special warnings and precautions for use.

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. Symptoms and Treatment of overdose
In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: All other therapeutic products, drugs for treatment of hyperkalemia and hyperphosphataemia. ATC code: V03AE02.

Mechanism of action
Velsone 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.

Pharmacodynamics
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.

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.

6.0 PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Tablet core:
Povidone, Sodium Chloride, Microcrystalline Cellulose, Zinc Stearate

Film-coat:
Opadry Complete Film Coating System 06F690000 Clear

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
Please refer to the expiry date on the product labels.

6.4. Special precautions for storage
Store below 30°C. Protect from moisture.

6.5. Nature and contents of containers
White Opaque HDPE bottle with White Opaque Polypropylene CR cap packed in the outer carton.

6.6. Special precautions for disposal
No special requirement.

7. MANUFACTURER
Manufactured by:
Novugen Pharma Sdn.Bhd.
No.27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
Negeri Sembilan, Malaysia

Product Registration Holder:
Novugen Pharma Sdn. Bhd.
No. 3, Jalan Jururancang U1/21,
Hicom Glenmarie Industrial Park,
40150, Shah Alam,
Selangor, Malaysia

Date of revision:
11/01/2023

3250000243