PRODUCT INFORMATION

Velphoro®

NAME OF THE MEDICINE

VELPHORO
Sucroferric oxyhydroxide

Chemical structure
Mixture of polynuclear iron(III)-oxyhydroxide, sucrose, pregelatinised maize starch and potato starch

Molecular formula: pn-FeOOH + x $C_{12}H_{22}O_{11}$ + y $(C_6H_{10}O_5)_n$

DESCRIPTION

Sucroferric oxyhydroxide is a brown amorphous powder, which is odourless, slightly sweet and practically insoluble in water.

Velphoro tablets are brown, round, flat-faced, chewable tablets embossed with PA500 on one side. The tablets contain 2.5 g sucroferric oxyhydroxide, equivalent to 500 mg iron. The tablets also contain the following inactive ingredients; woodberry flavour, neohesperidin-dihydrochalcone, magnesium stearate and - anhydrous colloidal silica.

The active ingredient sucroferric oxyhydroxide contains 750 mg sucrose and 700 mg starches.

PHARMACOLOGY

Pharmacodynamic Properties

Mechanism of Action

Velphoro contains a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches. Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the gastrointestinal tract.

Serum phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.

Pharmacokinetic Properties

Velphoro works by binding phosphate in the GI tract and thus the serum concentration is not relevant for its efficacy. Due to the insolubility and degradation characteristics of Velphoro,

no classical pharmacokinetic studies can be carried out, e.g. determination of the distribution volume, area under the curve, mean residence time, etc.

In two Phase 1 studies, it was concluded that the potential for iron overload is minimal and no dose-dependent effects were observed in healthy volunteers. The sucrose and starch components of Velphoro can be digested to glucose and fructose, and maltose and glucose, respectively. These compounds can be absorbed in the blood. One tablet is equivalent to 1.4 g of carbohydrates.

Absorption

The active moiety of Velphoro, pn-FeOOH, is practically insoluble and therefore not absorbed. Its degradation product, mononuclear iron species, can however be released from the surface of pn-FeOOH and be absorbed.

The iron uptake from radiolabelled Velphoro drug substance, 2,000 mg in 1 day was investigated in 16 CKD patients (8 pre-dialysis and 8 haemodialysis patients) and 8 healthy volunteers with low iron stores (serum ferritin <100 mcg/L). In healthy subjects, the median uptake of radiolabelled iron in the blood was 0.43% on Day 21. In chronic kidney disease patients, the median uptake was minimal, 0.04% on Day 21. Blood levels of radiolabelled iron were very low and confined to the erythrocytes.

Distribution

Due to the insolubility and degradation characteristics of Velphoro, no classical pharmacokinetic studies can be carried out. Therefore, there is no data to determine the distribution of the drug.

Biotransformation

The active moiety of Velphoro, pn-FeOOH, is not metabolised. However, the degradation product of Velphoro, mononuclear iron species, can be released from the surface of polynuclear iron(III)-oxyhydroxide and be absorbed. Clinical studies have demonstrated that the systemic absorption of iron from Velphoro is low.

In vitro data suggest that the sucrose and starch components of the drug substance can be digested to glucose and fructose, and maltose and glucose, respectively. These compounds can be absorbed in the blood.

Excretion

In animal studies with rats and dogs administered ^{59}Fe-Velphoro drug substance orally, radiolabelled iron was recovered in the faeces but not the urine.

CLINICAL TRIALS

A randomised, open-label, active-controlled dose-ranging Phase 2 study over 6 weeks was performed in 154 patients on haemodialysis. Out of these, 128 patients received fixed

dosages of Velphoro, whereas 26 patients were on the comparator drug (sevelamer hydrochloride). Velphoro was shown to be pharmacologically active from 1,000 mg/day to 2,500 mg/day with significant dose-dependent serum phosphorus lowering effects. The 250 mg/day dose was ineffective. Velphoro doses of 1,000 or 1,500 mg/day appeared to be comparable to sevelamer hydrochloride 4,800 mg/day in lowering serum phosphorus. There were no patient-reported dose limiting treatment emergent adverse events (AEs). Mean changes in iron parameters (ferritin, TSAT and transferrin) and vitamins (A, D, E and K) were generally not clinically meaningful and showed no apparent trends across the treatment groups. Velphoro had a similar gastrointestinal AE profile to sevelamer hydrochloride and no dose-dependent trend in gastrointestinal events was observed.

One phase 3 clinical study has been performed in patients with chronic kidney disease (CKD) on dialysis to investigate the efficacy and safety of Velphoro in this population. This study was an open-label, randomised, active-controlled (sevelamer carbonate), parallel group study for up to 55 weeks and included 1,055 patients. Adult patients with hyperphosphataemia (serum phosphorus levels ≥1.94 mmol/L) were treated with Velphoro at a starting dose of 1,000 mg iron/day followed by an 8-week dose titration period. Non-inferiority to sevelamer carbonate was determined at week 12. Subjects were continued on their study medication from week 12 to week 55. From week 12 to 24, dose titrations were allowed for both tolerability and efficacy reasons.

In a subpopulation of 93 haemodialysis patients, the Velphoro maintenance dose (1,000 to 3,000 mg iron/day) was statistically significantly superior in sustaining the phosphorus lowering effect at Week 27 ($p<0.001$) compared with the non-effective low dose (250 mg/day) from Week 24 to Week 27 (see Table 1 below).

Table 1 :

Mean (SD) Serum Phosphorus and Change from Baseline to End of Treatment. PES (N=93)		
	Mean (SD) Serm Phosphorus (mmol/L)	
	Velphoro Maintenance Dose (1,000 to 3,000 mg/day) (N=44)	Velphoro Low Dose (250 mg/Day) (N=39)
Week 24 (BL)	1.5 (0.33)	1.6 (0.37)
Week 25	1.5 (0.30)	2.0 (0.46)
Week 26	1.5 (0.39)	2.1 (0.62)
Week 27/End of Treatment	1.6 (0.35)	2.2 (0.53)
Change from BL to End of Treatment	0.1 (0.40)[(1)]	0.6 (0.47)

[1] $p<0.001$ for the difference in least square means of the change from BL to Week 27/End of Treatment (LOCF principle) between Velphoro maintenance dose and low dose using a covariance analysis (MIXED Model).

Notes BL is Week 24 or latest value available before Week 24 when Week 24 result is missing; End of Teatment is Week 27 value or includes the latest evaluable measurement after Week 24 (i.e., LOCF).

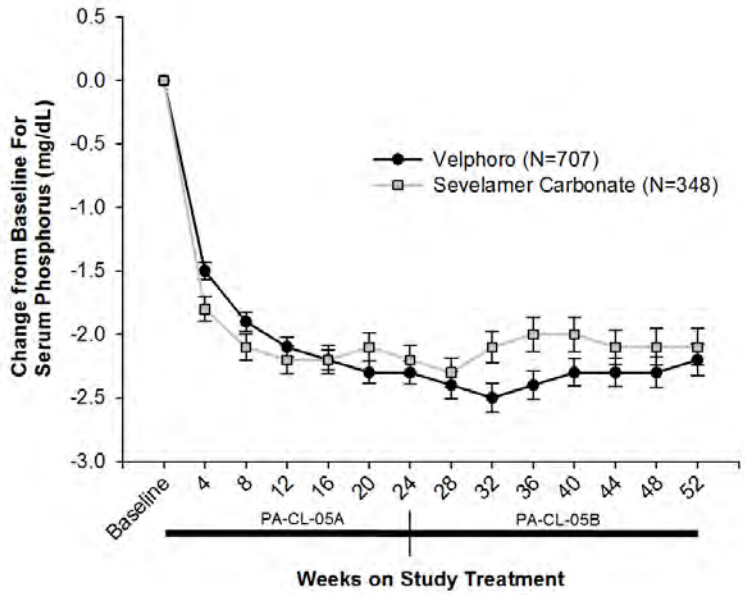
Bl = Baseline; LOCF = Last observation carried forward: PES = Primary efficacy set; SD = Standard deviation

Mean serum phosphorus levels were 2.5 mmol/L at baseline and 1.8 mmol/L at week 12 for Velphoro (reduction by 0.7 mmol/L). Corresponding levels for sevelamer carbonate at

baseline were 2.4 mmol/L and 1.7 mmol/L at week 12 (reduction by 0.7 mmol/L), respectively.

The serum phosphorus reduction was maintained over 52 weeks. Serum phosphorus levels and calcium-phosphorus product levels were reduced as a consequence of the reduced dietary phosphate absorption.

The mean daily dose of Velphoro over 52 weeks of treatment was 1,650 mg iron (3.3 tablets) and the mean daily dose of sevelamer carbonate was 6,960 mg (8.7 tablets).The age, gender, race, or dialysis did not affect the efficacy of Velphoro.



Notes: The Week 24 to Week 27 maintenance dose versus low dose period is not shown in the figure.
SEM = Standard error of the mean.

Figure 1 Mean (SEM) Change from Baseline in Serum Phosphorus over Time in Study PA-CL-05A and Extension Study PA-CL-05B

INDICATIONS

Velphoro is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease (CKD) on dialysis.

CONTRAINDICATIONS

The use of the drug is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in **DESCRIPTION** above.
- Haemochromatosis and any other iron accumulation disorders.

PRECAUTIONS

Patients with a recent history (of 3 months) of peritonitis, significant gastric or hepatic disorders, and patients with major gastrointestinal surgery have not been included in clinical studies with Velphoro. Velphoro should only be used in these patients following careful assessment of benefit/risk.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Use in Pregnancy (Category B3)
There are no available clinical data from the use of Velphoro on exposed human pregnancies.

Reproductive and developmental toxicity studies in animals revealed no risk with respect to pregnancy, parturition or postnatal development. However, a maternotoxic dose of Velphoro at 5 times the maximum clinical dose was associated with reduced fetal weight and delayed ossification in a rabbit embryofetal development study. A No-Effect Level was established at 2.5 times the maximum clinical dose.

Velphoro should only be used by pregnant women if clearly needed following careful assessment of benefit/risk.

Use in Lactation
There are no available clinical data from the use of Velphoro in lactating women.

Since absorption of iron from Velphoro is minimal (see **Pharmacokinetic Properties**), excretion of iron from Velphoro in breast milk is unlikely. A decision on whether to continue breast-feeding or to continue therapy with Velphoro should be made taking into account the benefit of breast-feeding to the child and the benefit of Velphoro therapy to the mother.

Paediatric Use
The safety and efficacy of Velphoro in children below the age of 18 years has not yet been established. No data are available.

Effects on fertility
There are no data on the effect of Velphoro on fertility in humans. No adverse effects on mating performance, fertility, and litter parameters were noted following treatment of rats with Velphoro at up to 20 times the maximum clinical dose.

Genotoxicity
Nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

Carcinogenicity
Carcinogenicity studies were performed in mice and rats. There was no clear evidence of a carcinogenic effect in mice. Mucosal hyperplasia, with diverticulum/cyst formation was observed in the colon and caecum of mice after 2 years treatment, but no diverticula/cystes were seen in long term studies in rats or dogs.

In rats only mucosal hyperplasia in the large intestine was seen. There was a slightly increased incidence of benign C-cell adenoma in the thyroid of male rats at 12 times the maximum clinical dose that is most likely an adaptive response to the pharmacological effect of Velphoro

Effects on Ability to Drive and Use Machines
No studies on the effects on ability to drive and use machines have been performed.

INTERACTIONS WITH OTHER MEDICINES

Drug-drug interaction studies have been conducted in healthy male and female subjects with losartan, furosemide, digoxin, warfarin, and omeprazole. Concomitant administration of Velphoro did not affect the bioavailability of these drugs as measured by the area under the curve (AUC).

Data from clinical studies have shown that Velphoro does not affect the lipid lowering effects of HMG-CoA reductase inhibitors (e.g. atorvastatin and simvastatin).

In vitro studies showed significant drug interaction (adsorption by Velphoro) with paricalcitol and doxercalciferol. However, data from clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D analogues. Serum vitamin D and 1,25-dihydroxy Vitamin D levels remained unchanged.

In vitro studies showed significant drug interaction (adsorption by Velphoro) with alendronate, cephalexin, doxycycline and levothyroxine. No clinical data is available at present. It is recommended that these drugs should be administrated at least 1 hour before or at least 2 hours after intake of Velphoro.

In vitro studies with the following drugs did not show any relevant interaction: cinacalcet, ciprofloxacin,clopidogrel, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, pioglitazone and quinidine. However, clinical data are not available at present.

Velphoro can cause discoloured (black) stool. Discoloured (black) stool may visually mask gastrointestinal (GI) bleeding. However, Velphoro does not affect guaiac based (Hemoccult) or immunological based (iColo Rectal and Hexagon Obti) faecal occult blood tests.

Concomitant treatment with antacids containing aluminium, magnesium or calcium and oral iron therapies as well as phosphate binders has not been investigated.

When administering any medicinal product that is known to interact with iron, the medicinal product should be administered at least one hour before or two hours after Velphoro.

ADVERSE EFFECTS

The safety of Velphoro has been investigated in 2 active controlled clinical studies: a 6-week dose finding study and a safety and efficacy study of up to 55 weeks. A total of 778 patients on haemodialysis and 57 patients on peritoneal dialysis were treated with treatment duration

of up to 55 weeks. Velphoro had a similar adverse drug reaction (ADR) profile to sevelamer and no dose-dependent trends were observed.

Table 2 below reports the most common adverse events occurring in at least 5% of patients in either group.

Table 2 Frequency of Adverse Events >5% in the Clinical Trials

	PA-CL-03A (N=154)		PA-CL-05A/PA-CL-05B (N=1055)	
MedDRA Preferred Term	**Velphoro (N=128) %**	**Sevelamer (N=26) %**	**Velphoro (N=707) %**	**Sevelamer (N=348) %**
Gastrointestinal disorders				
Diarrhoea	5.5%	11.5%	23.6%	11.5%
Faeces discoloured	11.7%	0.0%	16.1%	0.3%
Nausea	0.8%	3.8%	9.8%	14.4%
Vomiting	2.3%	3.8%	5.9%	9.2%
Constipation	3.1%	0.0%	5.1%	8.3%
Metabolism and nutrition disorders				
Hyperphosphataemia	7.8%	7.7%	16.0%	12.6%
Hypophosphataemia	18.0%	11.5%	5.7%	8.3%
Hyperkalaemia	0.8%	0.0%	5.4%	7.2%
Hypocalcaemia	0.0%	0.0%	4.7%	6.3%
Hypercalcaemia	5.5%	7.7%	3.8%	2.9%
Infections and infestations				
Nasopharyngitis	1.6%	0.0%	4.1%	5.7%
Upper respiratory tract infection	0.0%	0.0%	3.5%	5.2%
Vascular disorders				
Hypertension	3.9%	3.8%	11.2%	11.8%
Hypotension	0.8%	11.5%	5.8%	8.9%
General disorders and administration site conditions				
Pyrexia	1.6%	3.8%	4.5%	5.5%
Chest pain	0.0%	0.0%	3.3%	5.7%
Musculoskeletal and connective tissue disorders				
Muscle spasms	6.3%	0.0%	6.8%	7.8%
Injury, poisoning and procedural complications				
Arteriovenous fistula site complication	0.8%	0.0%	4.5%	7.5%
Nervous system disorders				
Headache	1.6%	0.0%	6.1%	5.7%
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0.8%	0.0%	4.0%	5.5%
Blood and lymphatic system disorders				
Anaemia	2.3%	0.0%	4.0%	8.3%
Endocrine disorders				
Hyperparathyroidism secondary	0.0%	0.0%	4.2%	8.9%

Notes: Velphoro treatment group in PA-CL-05A/PA-CL-05B also includes adverse events occurring in PA-CL-05A Stage 2.
Presentation is by decreasing frequency in Velphoro in PA-CL-05A/PA-CL-05B followed by PA-CL-03A.
N is the number of subjects, each subject counts only once for each adverse event.

Adverse drug reactions reported from the use of Velphoro at doses from 250 mg iron/day to 3,000 mg iron/day in these patients (n=835) are summarised in Table 3.

Table 3 Adverse Drug Reactions Detected in Clinical Trials

System Organ Class	Very Common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)
Gastrointestinal Disorders	Diarrhoea* Discoloured faeces **	Nausea Constipation Vomiting Dyspepsia Abdominal pain Flatulence Tooth dicolouration***	Abdominal distension Gastritis Abdominal discomfort Dysphagia Gastro-oesophageal reflux disease Tongue discolouration***
Metabolism and Nutrition Disorders			Hypercalcaemia Hypocalcaemia
General Disorders and Administration Site Conditions		Product taste abnormal	Fatigue
Skin and Subcutaneous Tissue Disorders			Pruritus Rash
Nervous System Disorders			Headache
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea

* Diarrhoea occurred in 11.6% of patients in clinical trials. In the 55 weeks long term studies, the majority of these treatment-related diarrhoea adverse events were mild and transient, occurred early during treatment initiation and led to treatment discontinuation in only 3.1% of the patients.

** Discoloured faeces were also very commonly seen (15% of patients) as expected with oral preparations containing iron.

***Some cases of temporary discoloration of tooth and tongue were also seen.

Post marketing experience

No post-marketing experience to date.

DOSAGE AND ADMINISTRATION

Tablets must be taken with meals, chewed and not swallowed whole. The tablets may be crushed as an aid to chewing.

Patients receiving Velphoro should adhere to their prescribed diets.

Starting Dose

The recommended starting dose of Velphoro is 1,500 mg iron per day (3 tablets). Velphoro is for oral administration only and must be taken with meals.

Titration and Maintenance
Serum phosphorus levels must be monitored and the dose of Velphoro up or down titrated in increments of 500 mg (1 tablet) per day every 2-4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring afterwards.

In clinical practice, treatment will be based on the need to control serum phosphorus levels, though patients who respond to Velphoro therapy usually achieve optimal serum phosphorus levels at doses of 1,500 mg-2,000 mg iron per day (3 to 4 tablets).

Maximum Tolerated Daily Dose
The maximum recommended dose is 3,000 mg iron (6 tablets) per day.

Paediatric Population
The safety and efficacy of Velphoro in children below the age of 18 years has not yet been established. No data are available.

Elderly
Velphoro has been administered to over 245 seniors (≥65 years of age) according to the approved dosing regimen. Of the total number of subjects in clinical studies of Velphoro, 29.7 % were aged 65 and over, while 8.7% were aged 75 and over. No special dosage and administration guidelines were applied to seniors in these studies and the dosing schedules were not associated with any significant concerns.

Renal Impairment
Velphoro is indicated for the control of serum phosphorus levels in patients withchronic kidney disease on dialysis. There is no clinical data available with Velphoro in patients with earlier stage of renal impairment.

Hepatic Impairment
Generally, patients with severe hepatic impairment were excluded from participating in clincal studies with Velphoro. However, no evidence of hepatic impairment or significant alteration of hepatic enzymes were observed in the clinical studies with Velphoro.

Method of Administration
Velphoro is a chewable tablet that must be taken with meals. In order to maximise the adsorption of dietary phosphate, the total daily dose should be divided across the meals of the day. Patients are not required to drink more fluid than they normally would. Tablets must be chewed and not swallowed whole. Tablets may be crushed.

If one or more doses are missed, the normal dose of the medication should be resumed with the next meal.

OVERDOSAGE

No case of overdose with Velphoro has been reported. Since the absorption of iron from Velphoro is low, the risk of systemic iron toxicity is negligible. Any instances of overdose (eg, hypophosphatemia) due to phosphate binder overdose should be treated by standard clinical practice.

PRESENTATION AND STORAGE CONDITIONS

Presentations

Each Velphoro chewable tablet contains 2,500 mg of sucroferric oxyhydroxide (equivalent to 500 mg iron).

The tablets are supplied in high density polyethylene (HDPE) bottle with child-resistant closure and foil induction seal, containing a molecular sieve desiccant and cotton. Pack sizes of 30 or 90 chewable tablets.

The tablets are supplied in blister, each blister containing 6 chewable tablets. Pack sizes of 30 or 90 chewable tablets.

Not all pack sizes may be marketed.

Storage conditions

Store below 30^{o}C

Store in the original package in order to protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

27/11/2014