VELPHORO®

sucroferric oxyhydroxide

1 pill per meal*

*Starting dose 1 pill per meal, 3 times per day

Vifor Fresenius Medical Care
Renal Pharma

SINCE 1921

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in June 2016

1. NAME OF THE MEDICINAL PRODUCT

Velphoro 500 mg chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains 500 mg iron as sucroferric oxyhydroxide also known as a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Red-Brown, circular tablets embossed with PA500 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Velphoro is indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD).

Velphoro 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, or calcimimetics to control the development of renal bone disease.

4.2 Posology and method of administration

Posology

Starting dose

The recommended starting dose of Velphoro is 1,500 mg iron (3 tablets) per day, divided across the meals of the day. Velphoro is for oral administration only and must be taken with meals.
Patients receiving Velphoro should adhere to their prescribed diets.

Titration and maintenance

Serum phosphorus levels must be monitored and the dose of Velphoro up or down titrated in increments of 500 mg iron (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).

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

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 population (≥65 years of age)

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 dose 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 adult CKD patients on HD or PD. There is no clinical data available

with Velphoro in patients with earlier stages of renal impairment.

Hepatic impairment

Generally, patients with severe hepatic impairment were excluded from participating in clinical 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

Oral use.
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Haemochromatosis and any other iron accumulation disorders.

4.4 Special warnings and precautions for use

Peritonitis, gastric and hepatic disorders and gastrointestinal surgery

Patients with a recent history of peritonitis (within the last 3 months), 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.

Information about sucrose and starches (carbohydrates)

Velphoro contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

Velphoro contains starches. Patients with allergy to gluten or diabetics should take notice that one tablet of Velphoro is equivalent to 0.116 bread units (equivalent to approximately 1.4 g of carbohydrates).

Discoloured stool

Velphoro can cause discoloured (black) stool. Discoloured (black) stool may visually mask gastrointestinal bleeding (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Velphoro is almost not absorbed from the gastrointestinal tract. Although the potential for interactions with medicinal products seems low, for concomitant treatment with medicinal products with a narrow therapeutic window, the clinical effect and adverse events should be monitored, on initiation or dose-adjustment of either Velphoro or the concomitant medicinal product, or the physician should consider measuring blood levels. When administering any medicinal product that is already known to interact with iron (like alendronate and doxycycline) or has the potential to interact with Velphoro based only on in vitro studies like levothyroxine, the medicinal product should be administered at least one hour before or two hours after Velphoro.

In vitro studies with the following active substances did not show any relevant interaction: acetylsalicylic acid, cephalexin, cinacalcet, ciprofloxacin, clopidogrel, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, pioglitazone and quinidine.

Drug-drug interaction studies have only been performed in healthy volunteers. They have been conducted in healthy human male and female subjects with losartan, furosemide, digoxin, warfarin, and omeprazole. Concomitant administration of Velphoro did not affect the bioavailability of these medicinal products 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 addition, post-hoc analyses
from clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D
analogues. Vitamin D and 1,25-dihydroxy Vitamin D levels remained unchanged.

Velphoro does not affect guaiac based (Haemoccult) or immunological based (iColo Rectal and Hexagon Obti) faecal occult blood tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available clinical data from the use of sucroferric oxyhydroxide on exposed human pregnancies.

Reproductive and developmental toxicity studies in animals revealed no risk with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). Velphoro should only be used by pregnant women if clearly needed following careful assessment of benefit/risk.

Breast-feeding

There are no available clinical data from the use of Velphoro in breast-feeding women. Since absorption of iron from Velphoro is minimal (see section 5.2), 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.

Fertility

There are no data on the effect of Velphoro on fertility in humans. In animal studies, there were no adverse effects on mating performance, fertility, and litter parameters following treatment with Velphoro (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The current safety profile of Velphoro is based on a total of 778 patients on haemodialysis and 57 patients on peritoneal dialysis, who received Velphoro treatment of up to 55 weeks.

In these clinical trials, approximately 43% of patients experienced at least one adverse reaction during Velphoro treatment, which

were reported as serious adverse reactions in 0.36%. The majority of the adverse drug reactions (ADRs) reported from trials were gastrointestinal disorders, with the most frequently reported ADRs being diarrhoea and discoloured faeces (very common). The vast majority of these gastrointestinal disorders occurred early during treatment and abated with time with continued dosing. No dose-dependent trends were observed in the ADR profile of Velphoro.

Tabulated list of adverse reactions

ADRs 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 listed in Table 1.

Table 1 Adverse drug reactions detected in clinical trials

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Metabolism and nutrition disorders			Hypercalcaemia Hypocalcaemia
Nervous system disorders			Headache
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Diarrhoea* Discoloured faeces	Nausea Constipation Vomiting Dyspepsia Abdominal pain Flatulence Tooth discolouration	Abdominal distension Gastritis Abdominal discomfort Dysphagia Gastro-oesophageal reflux disease (GORD) Tongue discolouration
Skin and subcutaneous tissue disorders			Pruritus Rash
General disorders and administration site conditions		Product taste abnormal	Fatigue

Description of selected adverse reactions
*Diarrhoea
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 transient, occurred early during treatment initiation and led to treatment discontinuation in 3.1% of the patients.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedicl@moh.gov.il).

4.9 Overdose

Any instances of overdose of Velphoro should be treated by standard clinical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia; ATC code: V03AE05

Mechanism of action

Velphoro contains a mixture of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), 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.

Clinical efficacy

One phase 3 clinical study has been performed in patients with 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. 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. Treatment of patient sub-populations from week 24 to week 27 with maintenance dose of Velphoro (1,000 to 3,000 mg iron/day) or low dose (250 mg iron/day) of Velphoro demonstrated superiority of the maintenance dose.

In Study-05A, 1,055 patients on hemodialysis (N=968) or peritoneal dialysis (N=87) with serum phosphorus ≥1.94 mmol/L following a 2-4 week phosphate binder washout period, were randomized and treated with either Velphoro, at a starting dose of 1,000 mg/day (N=707), or active-control (sevelamer carbonate, N=348) for 24 weeks. At the end of week 24, 93 patients on hemodialysis whose serum phosphorus levels were controlled (<1.78 mmol/L) with Velphoro in the first part of the study, were re-randomized to continue treatment with either their week 24 maintenance dose (N=44 or a non-effective low dose control 250 mg/day, N=49) of Velphoro for a further 3 weeks.

Following completion of Study-05A, 658 patients (597 on hemodialysis and 61 on peritoneal dialysis) were treated in the 28-week extension study (Study-05B) with either Velphoro (N=391) or sevelamer carbonate (N=267) according to their original randomization.

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 55 weeks. Serum phosphorus levels and calcium-phosphorus product levels were reduced as a consequence of the reduced dietary phosphate absorption.

The response rates, defined as the proportion of subjects achieving serum phosphorus levels within the KDOQI (Kidney Disease Outcomes Quality Initiative) recommended range were 45.3% and 59.1% at week 12 and 51.9% and 55.2% at week 52, for Velphoro and sevelamer carbonate, respectively.

The mean daily dose of Velphoro over 55 weeks of treatment was 1,650 mg iron and the mean daily dose of sevelamer carbonate was 6,960 mg.

Paediatric population

No data available.

5.2 Pharmacokinetic properties

Velphoro works by binding phosphate in the gastrointestinal 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 2 Phase 1 studies, it was concluded that the potential for iron overload is minimal and no dose-dependent effects were observed in healthy volunteers.

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 absolute absorption studies in humans were not performed. Non-clinical studies in several species (rats and dogs) showed that systemic absorption was very low (≤1% of the administered dose).

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 estimated to be 0.43% (range 0.16 – 1.25%) on Day 21, in pre-dialysis patients 0.06% (range 0.008 – 0.44%) and in haemodialysis patients 0.02% (range 0 – 0.04%). Blood levels of radiolabelled iron were very low and confined to the erythrocytes.

Distribution

The distribution studies in humans were not performed. Non-clinical studies in several species (rats and dogs) showed that pn-FeOOH is distributed from the plasma to the liver, spleen and bone marrow, and utilized by incorporation into red blood cells.

In patients, absorbed iron is expected to be also distributed to the target organs, i.e. liver, spleen and bone marrow, and utilized by incorporation into red blood cells.

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.

Elimination

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.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects seen in the rabbit embryo-foetal development toxicity study (skeletal variations and incomplete ossificaton) are related to

exaggerated pharmacology, and likely not relevant for patients. Other reproduction toxicity studies showed no adverse effects.

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 this was considered a species-specific effect with no diverticula/cysts seen in long term studies in rats or dogs. In rats, there was a slightly increased incidence of benign C-cell adenoma in the thyroid of male rats given the highest dose of sucroferric oxyhydroxide. This is thought to be most likely an adaptive response to the pharmacological effect of the drug, and not clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Woodberry flavour
Neohesperidin-dihydrochalcone
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

Shelf life after first opening of the bottle: 45 days

6.4 Special precautions for storage

Store below 25^{0}C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with child-resistant polypropylene closure and foil induction seal, containing a molecular sieve desiccant and cotton. Pack sizes of 30 or 90 chewable tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

CTS Ltd.
4 Haharash St.
Hod-Hasharon 4524075
Israel

CTS ltd.
4 Haharash St.
Hod Hasharon
4524075 ISRAEL
www.cts.co.il
www.facebook.com/CTS.pharma

Side effect can be reported to the ministry of health using the online form for reporting side effects in the IL MOH website: www.health.gov.il

Vifor Fresenius Medical Care
Renal Pharma

SINCE 1921