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 (potato starch and pregelatinised maize starch) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Brown, circular tablets embossed with PA500 on one side. Tablets have a 20 mm diameter and a thickness of 6.5 mm.

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 D_3 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 – 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 and adolescents 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 248 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

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. See further information in section 4.4.

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 or crushed; tablets must not be swallowed whole.

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.
It may be harmful to the teeth.

Velphoro contains potato starch and pregelatinised maize starch. Patients with diabetes should take notice that one tablet of Velphoro is equivalent to approximately 1.4 g of carbohydrates (equivalent to 0.116 bread units).

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 reactions reported from trials were gastrointestinal disorders, with the most frequently reported adverse reactions 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 adverse reaction profile of Velphoro.

Tabulated list of adverse reactions

Adverse 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 listed in Table 1.
The reporting rate is classified as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).

Table 1 Adverse reactions detected in clinical trials

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders			Hypercalcaemia Hypocalcaemia
Nervous system disorders			Headache
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Diarrhoea* Faeces discoloured	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 diarrhoea adverse reactions were transient, occurred early during treatment initiation and led to treatment discontinuation in 3.1% of the patients.

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 via ZPTH-CS-CRC@zuelligpharma.com.

4.9 Overdose

Any instances of overdose of Velphoro (e.g. hypophosphataemia) 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 iron/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 iron/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.

Post-authorization data

A prospective, non-interventional, post-authorisation safety study (VERIFIE) has been conducted, evaluating the short- and long-term (up to 36 months) safety and effectiveness of Velphoro in adult patients on haemodialysis (n=1,198) or peritoneal dialysis (n=160), who were followed in routine clinical practice for 12 to 36 months (safety analysis set, N=1,365). During the study, 45% (n=618) of these patients were concomitantly treated with phosphate binder(s) other than Velphoro.

In the safety analysis set, the most common ADRs were diarrhoea and discoloured faeces, reported by 14% (n=194) and 9% (n=128) of patients, respectively. The incidence of diarrhoea was highest in the first week and decreased with duration of use. Diarrhoea was of mild to moderate intensity in most patients and resolved in the majority of patients within 2 weeks. Discoloured (black) faeces is expected for an oral iron-based compound, and may visually mask gastrointestinal bleeding. For 4 of the 40 documented concomitant gastrointestinal bleeding events, Velphoro-related stool discolouration was reported as causing an insignificant delay in diagnosis of gastrointestinal bleeding, without affecting patient health. In the remaining cases, no delay in diagnosis of gastrointestinal bleeding has been reported.

The results from this study showed that the effectiveness of Velphoro in a real-life setting (including concomitant use of other phosphate binders in 45% of patients), was in line with that observed in the phase 3 clinical study.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Velphoro in one or more subsets of the paediatric population in the treatment of hyperphosphataemia (see section 4.2 for information on paediatric use).

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 iron 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

3 years
Shelf life after first opening of the bottle: 45 days

6.4 Special precautions for storage

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

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.

Child-resistant aluminium/aluminium perforated unit-dose blister, each blister containing 6 chewable tablets. Pack sizes of 30 × 1 or multipack of 90 (3 packs of 30 × 1) 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. MANUFACTURERS

Manufactured by:
Vifor SA
Route de Moncor 10
CH-1752 Villars-sur-Glâne
Switzerland

Manufactured for:
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Rechenstrasse 37
CH-9014 St.Gallen
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8. MARKETING AUTHORISATION HOLDER

Fresenius Kabi (Thailand) Ltd.
Bangkok, Thailand

9. MARKETING AUTHORISATION NUMBER

10. DATE OF FIRST AUTHORISATION

11. DATE OF REVISION OF THE TEXT

11 May 2022