Product	Velphoro 90 Chewable Tablets	
Country	Singapore	
Manufacturer	VIF	
SAP Number	3004841-03S	**Min. Ver.:** 01
Manufacturer Identification Number	See SAP Number	
Fonts	Din (x-Höhe min. 1.43 mm)	
Dimensions	160 × 630 mm	

Colours / Flats
Black

Non-Printed Colours
Keyline / Cutter

Leserichtung > XXX

Leserichtung > XXX

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VELPHORO®

1. NAME OF THE MEDICINAL PRODUCT

Velphoro® (sucroferric oxyhydroxide) chewable tablet 500 mg iron.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Velphoro contains sucroferric oxyhydroxide corresponding to 500 mg iron.

The sucroferric oxyhydroxide contained in one tablet is comprised of polynuclear iron (III)-oxyhydroxide (containing 500 mg iron),750 mg sucrose and 700 mg starches (potato starch and pregelatinised maize starch).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

Red-brown, round, flat-faced 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 patients with end-stage renal disease (ESRD) on haemodialysis or peritoneal dialysis.

4.2 Posology and Method of Administration

Velphoro is for oral administration only.

Posology

Starting Dose
The recommended starting dose of Velphoro is 1,500 mg iron (3 tablets) per day administered as 1 tablet (500 mg iron) 3 times daily 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 iron (1 tablet) per day as needed every 1–2 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. In case of hypophosphatemia occurring during the titration and maintenance phase, Velphoro should be down titrated to achieve appropriate serum phosphorus levels.

Based on clinical studies, on average patients required 1,500 mg iron to 2,000 mg iron (3 to 4 tablets) a day to control serum phosphorus level.

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).

Special Populations

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

Elderly population (≥ 65 years of age)
Of the total number of subjects in two active-controlled clinical studies of Velphoro (n = 835), 29.7 % (n = 248) were aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal Impairment
Velphoro is indicated for the control of serum phosphorus levels in adult ESRD patients on haemodialysis or peritoneal dialysis. 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
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 and should adhere to their prescribed diets. Tablets must be chewed or crushed; tablets must not be swallowed whole.

4.3 Contraindications

The use of the drug is contraindicated in patients with:
- 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, gastrointestinal and hepatic disorders and gastrointestinal surgery
Patients with peritonitis, significant gastrointestinal 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 sucrose-isomaltase insufficiency should not take this medicinal product.

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 (GI) bleeding (see section 4.5).

Concomitant use of Velphoro with oral and intravenous iron products
In the Phase 3 study, concomitant intravenous but not oral iron use was allowed. Changes in iron parameters (e.g. increases in ferritin and TSAT, decreases in transferrin) which did not result in significant effects on haemoglobin and/or haematocrit values were observed in the Velphoro patients. Longer-term usage during the extension phase of the study did not show further significant changes in iron parameters. Velphoro should only be administered concomitantly with oral or intravenous iron supplementation after careful assessment of benefit/risk and periodic clinical monitoring of iron parameters should be performed.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Effects of other agents on the pharmacokinetics of Velphoro
Effect of concomitant medications administrated with Velphoro on its phosphate binding capacity was not measured.

Effect of Velphoro on the pharmacokinetics of other agents
Interaction studies have not been performed in patients on dialysis.

Five *in vivo* drug-drug interaction studies (n = approx. 40/study) have been conducted with losartan, furosemide, digoxin, warfarin, and omeprazole in healthy human male and female subjects receiving 1,000 mg Velphoro 3 times a day with meals. Velphoro did not affect the bioavailability of these drugs as measured by the area under the curve (AUC) when co-administered with Velphoro or given 2 hours later.

In vitro interactions were studied in aqueous solutions which mimic the physico-chemical conditions of the gastro-intestinal tract with or without the presence of phosphate (400 mg). The study was conducted at pH 3.0, 5.5 and 8.0 with incubation at 37°C for 6 hours.

Interaction has been observed in *in vitro* studies with the following drugs: alendronate, atorvastatin, doxercalciferol, doxycycline, levothyroxine and paricalcitol.

Levothyroxine should not be prescribed with Velphoro while doxycycline should be taken at least 1 hour before Velphoro.

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, clinical studies demonstrated no impact of Velphoro on iPTH lowering effect of oral Vitamin D analogues. Changes in Vitamin D and 1,25-dihydroxy Vitamin D levels are minimal and clinically insignificant.

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

Velphoro is almost not adsorbed from the gastrointestinal tract but may affect the bioavailability of other medicinal products. There are no empirical data on avoiding drug interactions between Velphoro and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separating the administration of the two drugs. The necessary 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. For concomitant treatment with medicinal products with a narrow therapeutic window, caution should be exercised and 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.

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy
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, embryonic/foetal development, parturition or postnatal development (see section 5.3). Because animal reproduction studies are not always predictive of human response, this drug 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 the patients experienced at least one adverse reaction during Velphoro treatment, and 0.36% of the adverse reactions were reported as serious. 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 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).

Post-marketing Experience
The safety profile of Velphoro has been confirmed in the post-authorisation safety study (PASS) VERIFIE (see section 5.1).

4.9 Overdose

No case of overdose has been reported. Since the absorption of iron from Velphoro is low, the risk of systemic iron toxicity is negligible. 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: All other therapeutic products; drugs for treatment of hyperkalaemia and hyperphosphataemia.

ATC code: V03AE05

Mechanism of Action
Velphoro contains sucroferric oxyhydroxide which is comprised 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 (GI) tract. The bound phosphate is eliminated with faeces.

Table 1
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)
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 treatment-related diarrhoea events were transient, occurred early during treatment initiation and led to treatment discontinuation in 3.1 % of the patients.

Both serum phosphorus levels and calcium-phosphorus product levels are reduced as a consequence of the reduced dietary phosphate absorption.

Clinical Efficacy and Safety
The ability of Velphoro to lower serum phosphorus in ESRD patients on dialysis was demonstrated in 2 randomised clinical trials: one 6-week open-label, randomised, active-controlled (sevelamer hydrochloride), parallel-group, dose-finding study; and one 55-week, open-label, randomised, active-controlled (sevelamer carbonate), parallel-group, safety and efficacy study.

6-Week, Open-label, Randomised, Active-control, Parallel-group, Dose-finding Study in Haemodialysis Patients with Hyperphosphataemia (PA-CL-03A)
A randomised, open-label, active-controlled dose-ranging Phase 2 study over 6 weeks was performed in 154 ESRD patients on haemodialysis who were hyperphosphatemic (serum phosphorus > 1.78 mmol/L but <2.50 mmol/L) following a 2-week phosphate binder washout period. These patients were randomized to receive Velphoro at 250 mg iron/day, 1,000 mg iron/day, 1,500 mg iron/day, 2,000 mg iron/day or 2,500 mg iron/day or active-control (sevelamer hydrochloride). Velphoro treatment was divided across meals, depending on dose. No dose titration was allowed. Within each of the groups, the serum phosphorus level at the end of treatment was compared to baseline value. Velphoro was shown to be efficacious ($p \leq 0.016$) for all doses except 250 mg iron/day. 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.

27-Week, Open-label, Randomised, Active-controlled, Parallel-group Safety and Efficacy Study (PA-CL-05A) followed by 28-week Safety Extension Study (PA-CL-05B) in Dialysis Patients with Hyperphosphataemia
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 PA-CL-05A, 1,055 patients on haemodialysis (N = 968) or peritoneal dialysis (N = 87) with serum phosphorus ≥1.94 mmol/L following a 2–4 week phosphate binder washout period, were randomised 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 PA-CL-05A, 658 patients (597 on haemodialysis and 61 on peritoneal dialysis) were treated in the 28-week safety extension study (Study 05B) with either Velphoro (N = 391) or sevelamer carbonate (N = 267) according to their original randomisation.

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 (see Figure 1).

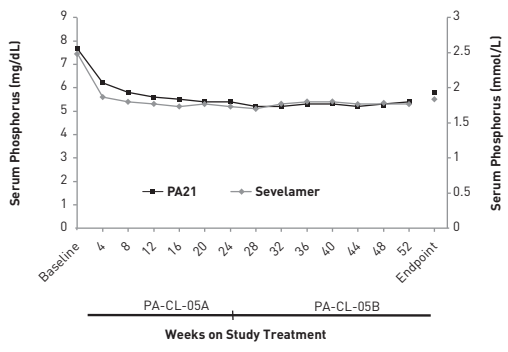

Figure 1
Mean (SEM) Serum Phosphorus Levels over Time in Study PA-CL-05A and Extension Study PA-CL-05B

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 Kidney Disease Outcomes Quality Initiative (KDOQI) 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.

Serum phosphorus levels declined rapidly during the first few weeks of the titration phase, remaining relatively constant thereafter. The phosphorus lowering effect of Velphoro was consistently maintained through 12 months of treatment (see Figure 2).

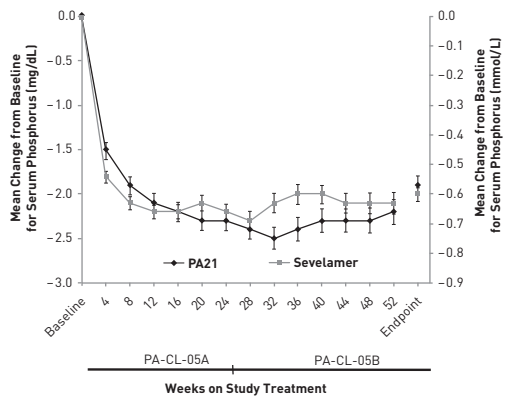

Figure 2
Mean (SEM) Change from Baseline in Serum Phosphorus over Time in Study PA-CL-05A and Extension Study PA-CL-05B
Note: The Week 24 to Week 27 maintenance dose versus low dose period is not shown in the figure.

Post-authorisation 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.

5.2 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 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 iron uptake from radiolabelled Velphoro active substance, 2,000 mg iron in 1 day was investigated in 16 chronic kidney disease (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 CKD 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 active 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 active 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, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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. The observed epithelial hyperplasia, which is also observed in rats, is postulated to be due to chronic local irritation from high amounts of intraluminal Velphoro in the GI tract. Epithelial hyperplasia was not observed in chronic dog studies. In rats, there was a slightly increased incidence of benign C-cell adenoma in the thyroid of male rats given the highest dose of PA21. This is thought to be most likely an adaptive response to the pharmacological effect of the medical product and not clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Velphoro is supplied as chewable tablets, 500 mg iron.

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

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.

Store in the original package.

6.5 Nature and Contents of Container

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.

Child-resistant aluminium/aluminium blister, each blister containing 6 chewable tablets. 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

Fresenius Kabi (Singapore) Pte Ltd
238A Thomson Road
#24-03/05 Novena Square Tower A
Singapore 307684

8. DATE OF REVISION OF THE PACKAGE INSERT

July 2022

Table 2
Composition of Velphoro

Component	Function	Quantity per Tablet (mg)	Quantity per Tablet (%)
Sucroferric oxyhydroxide (comprised of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches)	Active ingredient	2,500.00[1] (iron equiv. 500.00)	97.0 (19.4)
Woodberry flavour	Flavour	40.00	1.6
Neohesperidin dihydrochalcone	Sweetener	0.01	0.0004
Magnesium stearate	Lubricant	25.00	1.0
Silica (colloidal, anhydrous)	Flow aid	12.49	0.5

[1] Each tablet is adjusted to 500 mg iron.

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