AUSTRALIAN PRODUCT INFORMATION - VELPHORO® (SUCROFERRIC OXYHYDROXIDE) CHEWABLE TABLETS

1. NAME OF THE MEDICINE

Sucroferric oxyhydroxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Velphoro chewable tablet contains 500 mg iron, equivalent to 2500 mg sucroferric oxyhydroxide.

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

For the full list of excipients see **Section 6.1 LIST OF EXCIPIENTS.**

3. PHARMACEUTICAL FORM

Velphoro chewable tablets are brown, round, flat-faced, chewable 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 chronic kidney disease (CKD) on dialysis.

4.2. DOSE AND METHOD OF 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 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 to 2,000 mg iron per day (3 to 4 tablets).

If one or more doses are missed, the normal dose of the medication 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
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 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 with chronic 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 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
Velphoro is for oral administration only. Velphoro chewable tablet 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

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 LIST OF EXCIPIENTS**.
- Haemochromatosis and any other iron accumulation disorders.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

One tablet of Velphoro is equivalent to approximately 1.4 g of carbohydrates.

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

Use in the Elderly
Refer to **Section 4.2 DOSE AND METHOD OF ADMINISTRATION– Elderly**.

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 Laboratory Tests
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.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, 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: acetylsalicylic acid, cephalexin, cinacalcet, ciprofloxacin, clopidogrel, enalapril, hydrochlorothiazide, metformin, metoprolol, nifedipine, pioglitazone and quinidine. However, clinical data are not available at present.

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.

4.6. FERTILITY, PREGNANCY AND LACTATION

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.

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 **Section 5.2 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.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8. ADVERSE EFFECTS (UNDESIRABLE 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 1 below reports the most common adverse events occurring in at least 5% of patients in either group.

Table 1 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 2.

Table 2 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* Faeces discoloured **	Nausea Constipation Vomiting Dyspepsia Abdominal pain Flatulence Tooth discolouration***	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 discolouration of tooth and tongue were also seen.

Post marketing experience

No post marketing experience to date – until first undesirable effect from post-marketing spontaneous reporting.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. 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.

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 iron/day to 2,500 mg iron/day with significant dose-dependent serum phosphorus lowering effects. The 250 mg iron/day dose was ineffective. Velphoro doses of 1,000 or 1,500 mg iron/day appeared to be comparable to sevelamer hydrochloride 4,800 mg iron/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 iron/day) from Week 24 to Week 27 (see Table 3 below).

Table 3:

Mean (SD) Serum Phosphorus and Change from Baseline to End of Treatment. PES (N=93)		
	Mean (SD) Serum Phosphorus (mmol/l)	
	Velphoro Maintenance Dose (1,000 to 3,000 mg iron /day) (N=44)	Velphoro Low Dose (250 mg iron/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)

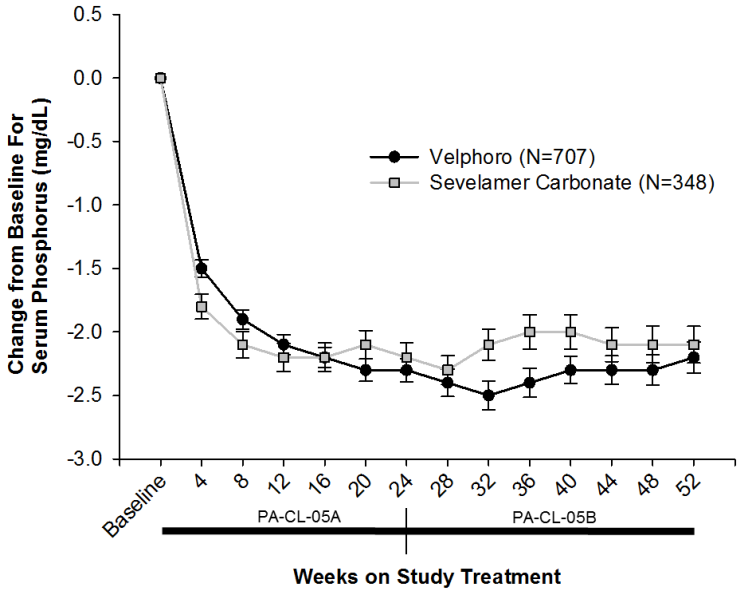
[1]$p<0.001$ for the difference in least square means of the change from BL to Week 27/End of Treatment (LOCF principle) between Velphoro maintenance dose and low dose using a covariance analysis (MIXED Model).
Notes BL is Week 24 or latest value available before Week 24 when Week 24 result is missing; End of Treatment 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.

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



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.

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. The mean duration of the observation period was 60 weeks and the mean duration of Velphoro therapy was 59.3 weeks.

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 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.

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 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 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.

Metabolism
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.

5.3. PRECLINICAL SAFETY DATA

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

The chewable tablets also contain the following inactive ingredients; woodberry flavour, neohesperidin-dihydrochalcone, magnesium stearate and colloidal anhydrous silica.

6.2. INCOMPATIBILITIES

Refer to **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Shelf life after first opening of the bottle: 90 days

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{o}C.

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

6.5. NATURE AND CONTENTS OF CONTAINER

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.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

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

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 $(C_6H_{10}O_5)_n$

CAS Number
12134-57-5

7. MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4

8. SPONSOR

Seqirus Pty Ltd
63 Poplar Rd,
Parkville VIC 3052
Australia
1800 642 865 (Within Australia).

9. DATE OF FIRST APPROVAL

27 November 2014

10. DATE OF REVISION

18 March 2024

Summary Table of Changes

Section	Change
8	Update to sponsor details