เอกสารกำกับยาภาษาอังกฤษ

(เหมือนกันทุกขนาดบรรจุ)

1. PRODUCT NAME

Fosrenol 250 mg, Fosrenol 500 mg, Fosrenol 750 mg, Fosrenol 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains lanthanum carbonate hydrate corresponding to 250 mg, 500 mg 750 mg or 1000 mg lanthanum.

For a full list of excipients, see **"List of excipients"**

3. PHARMACEUTICAL FORM

Chewable tablet

250 mg tablets: white, round, beveled-edge flat tablets debossed with 'S405/250' on one side.
500 mg tablets: white, round, beveled-edge flat tablets debossed with 'S405/500' on one side.
750 mg tablets: white, round, beveled-edge flat tablets debossed with 'S405/750' on one side.
1000 mg tablets: white, round, beveled-edge flat tablets debossed with 'S405/1000' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fosrenol is indicated as a phosphate binding agent for use in the control of hyperphosphataemia in chronic renal failure patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Fosrenol is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels $\geq$ 1.78 mmol/L in whom a low phosphate diet alone is insufficient to control serum phosphate levels.

4.2 Posology and method of administration

Fosrenol is for oral administration.

Fosrenol tablets must be chewed completely before swallowing. The tablets may be crushed as an aid to chewing. Intact tablets must not be swallowed whole.

Adults, including elderly (> 65 years)

Fosrenol should be taken with or immediately after food, with the daily dose divided between the meals. Patients should adhere to recommended diets in order to control phosphate and fluid intake. Fosrenol is presented as a chewable tablet therefore avoiding the need to take additional fluid. The dose is titrated every 2-3 weeks until an acceptable serum phosphorus level is reached. Serum phosphorus

levels are monitored as needed during dose titration and on a regular basis thereafter. Control of serum phosphate level has been demonstrated at doses starting from 750-1500 mg with most patients achieving acceptable serum phosphate levels at 1500-3000 mg lanthanum per day. The maximum dose studied in clinical trials, in a limited number of patients, is 3750 mg. Patients who respond to lanthanum therapy; usually achieve acceptable serum phosphate levels at doses of 1500-3000 mg lanthanum per day.

Most CKD5D patients require a total daily dose between 1500 mg and 3000 mg to reduce serum phosphorus levels. Doses are generally well-tolerated in increments of 750 mg/day. If hypophosphatemia develops during treatment, Fosrenol should be temporarily discontinued.

Children and Adolescents

The safety and efficacy of Fosrenol has not been established in patients below the age of 18 years (see section 4.8 and 5.1). Currently available data are described in sections 5.1 and 5.2, but no recommendation on posology can be made.

Hepatic impairment

The effect of hepatic impairment on Fosrenol pharmacokinetics has not been assessed. Due to its mechanism of action and the lack of liver metabolism doses in hepatic impairment should not be modified, but patients should be monitored carefully (see **"Special warnings and precautions for use"** and **"Pharmacokinetic properties"**).

4.3 Contraindications

Hypersensitivity to lanthanum carbonate hydrate or to any ingredient in the formulation.

Hypophosphataemia.

Fosrenol is contraindicated in patients with bowel obstruction, ileus and faecal impaction.

4.4 Special warnings and precautions for use

Tissue deposition of lanthanum has been shown with Fosrenol in animal studies. In 105 bone biopsies from patients treated with Fosrenol, some for up to 4.5 years, rising levels of lanthanum were noted over time (see **"Pharmacodynamic properties"**). No clinical data are available on deposition of lanthanum in other human tissues.

The use of Fosrenol in clinical studies beyond 2 years is currently limited. However, treatment of subjects with Fosrenol for up to 6 years has not demonstrated a change in the benefit/risk profile.

There have been cases of gastrointestinal obstruction, ileus, subileus, and gastrointestinal perforation reported in association with lanthanum, some requiring surgery or hospitalization (see "Undesirable effects). Some of the cases are found to have lanthanum deposition or Product residues in the gastrointestinal tract. Lanthanum deposition in gastroduodenal mucosa is demonstrated endoscopically as whitish lesions of different sizes and shapes. Also, various pathological features were identified in gastroduodenal mucosa with lanthanum deposition, such as chronic or active inflammation, glandular atrophy, regenerative changes, foveolar hyperplasia, intestinal metaplasia and neoplasia.

Exercise caution in all patients predisposed to gastrointestinal obstruction, ileus, subileus, and perforation; for example those with altered gastrointestinal anatomy) e.g., diverticular disease, peritonitis, history of gastrointestinal surgery, gastrointestinal cancer and gastrointestinal ulceration) hypomotility disorders (e.g., constipation, diabetic gastroparesis) and when used with medications known to potentiate these effects. Some cases were reported in patients with no history of gastrointestinal disease.

During treatment with lanthanum carbonate, physicians and patients should remain vigilant for signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distention which may indicate bowel obstruction, ileus or subileus.

Treatment with lanthanum carbonate should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal signs and symptoms.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in Fosrenol clinical studies

Fosrenol tablets must be chewed completely and not swallowed whole. Serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed tablets (see "**Posology and method of administration**").

Patients with renal insufficiency may develop hypocalcaemia. Fosrenol does not contain calcium. Serum calcium levels should therefore be monitored at regular time intervals for this patient population and appropriate supplement given.

No studies have been done in patients with hepatic impairment. Although lanthanum is not metabolized, it is excreted in the bile, and therefore caution should be exercised in patients with hepatic impairment or biliary obstruction

Conditions resulting in a marked reduction of bile flow may be associated with incrementally slower elimination of lanthanum, which may result in higher plasma levels and increased tissue deposition of lanthanum (see **"Pharmacokinetic properties"** and **"Preclinical safety data"**). As the liver is the principal organ of elimination of absorbed lanthanum monitoring of liver function tests is recommended.

Safety and efficacy of Fosrenol have not been established in children and adolescents; use in children and adolescents is not recommended (see **"Posology and method of administration"**).

Fosrenol should be discontinued if hypophosphataemia develops.

Fosrenol has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures.

Renal impairment

Patients with renal impairment may develop hypocalcaemia. Serum calcium levels should therefore be monitored at regular intervals in this patient population and appropriate supplements should be given.

4.5 Interaction with other medicinal products and other forms of interactions

The drug interactions profile of Fosrenol is characterized by the potential of lanthanum to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups).

Fosrenol has a low potential for systemic drug/drug interactions because of the very low bioavailability of lanthanum and because it is not a substrate or inhibitor of major cytochrome P450 enzyme groups involved in drug metabolism (CYP1A2, CYP2D6, CYP3A4/5, CYP2C9/10, and CYP2C19).

In a clinical study, it was demonstrated that Fosrenol dose not alter gastric pH. Therefore, Fosrenol drug interactions based on altered gastric pH are not expected.

Lanthanum carbonate hydrate may increase gastric pH. It is recommended that compounds, which are known to interact with antacids, should not be taken within 2 hours of dosing with Fosrenol (e.g. chloroquine, hydroxychloroquine and ketoconazole)

Citrate did not increase the absorption of lanthanum.

There was no evidence from non-clinical and clinical studies that lanthanum affected the intestinal absorption of fat-soluble vitamins (A, D, E and K) or other nutrients.

Coadministration of Fosrenol (1000 mg three times daily for one day) with calcitriol (2 x 0.5 mcg) to healthy subjects did not significantly alter peak concentrations or overall extent of absorption of calcitriol (1,25-dihydroxyvitamin D_3).

There is potential for Fosrenol to interact with other compounds subject to reduced absorption when coadministered with antacids (e.g., aluminium-, magnesium-, or calcium- based). Therefore, such compounds should not be taken within 2 hours of dosing with Fosrenol.

In an *in vitro* investigation, lanthanum did not form insoluble complexes when mixed in simulated gastic fluid with warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril. Clinical studies have shown that Fosrenol administered 30 minutes earlier did not alter the pharmacokinetics of oral warfarin, digoxin, or metoprolol.

However, interactions with drugs such as tetracycline and doxycycline are theoretically possible and if these compounds are to be co-administered, it is recommended that they are not to be taken within 2 hours of dosing with Fosrenol

Coadministration of Fosrenol with quinolone antibiotics may reduce the extent of their absorption as a result of complex formation. The bioavailability of oral ciprofloxacin decreased approximately 50% when taken together with Fosrenol in a single-dose study in healthy volunteers. It is recommended that oral quinolone antibiotics are taken at least 2 hours before or 4 hours after Fosrenol.

The bioavailability of levothyroxine decreased approximately 40% when taken together with Fosrenol. Therefore, thyroid hormone replacement therapy should not be taken within 2 hours of dosing with Fosrenol. Closer monitoring of Thyroid Stimulating Hormone (TSH) levels is recommended in patients receiving both medicinal products.

4.6 Fertility, Pregnancy and lactation

Fertility

Treatment with Fosrenol at oral doses up to 2000 mg(salt)/kg/day produced no effects on fertility in male or female rats.

Pregnancy

There are no adequate and well-controlled studies of Fosrenol in pregnant women. Fosrenol is not recommended for use during pregnancy.

One study in rats showed reproductive foetotoxicity (delayed eye opening and sexual maturation) and reduced pup weights at high doses (see **"Preclinical safety data"**). The potential risk for humans is unknown.

Lactation

It is unknown whether lanthanum is excreted in human breast milk. The excretion of lanthanum in milk has not been studied in animals. Caution should be used in taking a decision whether to continue/ discontinue breast feeding or to continue/discontinue therapy with Fosrenol, taking into account the potential benefit of breast feeding to the child and the potential benefit of Fosrenol therapy to the nursing mother.

4.7 Effects on ability to drive and use machines

Fosrenol may induce dizziness and vertigo, which may impair the ability to drive and use machinery.

4.8 Undesirable effects

The most commonly reported adverse drug reactions, with the exception of headache and allergic skin reactions, are gastrointestinal in nature; these are minimized by taking Fosrenol with food and generally abated with time with continued dosing (see section 4.2).

The following convention was used for frequency of adverse drug reactions: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to < 1/1,000); Very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and Infestations	
Uncommon	Laryngitis
Not known	Gasroenteritis
Blood and lymphatic system disorders	
Uncommon	Eosinophilia
Endocrine disorders	
Uncommon	Hyperparathyroidism
Metabolism and nutrition disorders	
Common	Hypocalcaemia
Uncommon	hyperglycaemia, hyperphosphataemia, hypophosphataemia, anorexia, appetite

	increased
Not known	Hypercalcaemia, decreased appetite
Nervous system disorders	
Very Common	Headache
Uncommon	Taste alteration
Not known	Dizziness
Ear and Labyrinth disorders	
Uncommon	Vertigo
Gastrointestinal disorders	
Very Common	Abdominal pain, diarrhea, nausea, vomiting
Common	Constipation, dyspepsia,
Uncommon	Eructation, indigestion, irritable bowel syndrome, dry mouth, oesophagitis, stomatitis, loose stools, tooth disorder, gastrointestinal disorder NOS*, ileus, subileus, intestinal obstruction
Not known	Flatulence
Rare	Intestinal perforation
Skin and subcutaneous tissue disorders	
Very common	Allergic skin reactions (including skin rashes, urticaria, and pruritus)
Uncommon	Alopecia, sweating increased
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia, myalgia, osteoporosis
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue, malaise, , pain, thirst
Rare	Tooth injury
Not known	Chest pain, oedema peripheral
Investigations	
Uncommon	Blood aluminium increased, increase in GGT, increases in hepatic transaminases, alkaline phosphatase increased, weight decrease.

* Not otherwise specified

Post marketing experience: During post-approval use of Fosrenol, cases of Allergic Skin Reactions (including skin rashes, urticarial and pruritus) have been reported which show a close temporal relationship to lanthanum carbonate therapy. In clinical trials, Allergic Skin Reactions were seen in both Fosrenol and placebo/active comparator groups at a frequency of Very Common (≥1/10).

Although there have been a number of additional isolated reactions reported, none of these reactions are considered unexpected in this patient population.

Transient QT changes have been observed but these were not associated with an increase of cardiac adverse events.

Paediatric population

Frequency, type and severity of adverse reactions in children have not been fully established. In particular, uncertainty exists on the accumulation in bone and risk of growth retardation with treatment in children.

4.9 Overdose

No case of overdose has been reported. The highest daily dose of lanthanum administered to healthy volunteers during Phase I studies was 4718 mg given for 3 days. The adverse events seen were mild to moderate and included nausea and headache.

4.10 Drug abuse and dependence

Fosrenol is not known for abuse or dependence.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia.

ATC code: V03A E03Fosrenol contains lanthanum carbonate hydrate. The activity of lanthanum carbonate hydrate as a phosphate binder is dependent on the high affinity of lanthanum ions, which are released from the carbonate salt in the acid environment of the stomach, for dietary phosphate. Insoluble lanthanum phosphate is formed which reduces the absorption of phosphate from the gastro-intestinal tract.

A total of 1130 patients with chronic renal failure treated with maintenance haemodialysis or CAPD were studied in two phase II and two phase III studies. Three studies were placebo controlled (1 fixed dose and 2 titrated dose designs) and one included calcium carbonate as an active comparator. During these studies, 1016 patients received lanthanum carbonate, 267 received calcium carbonate and 176 received placebo.

After 4 weeks of treatment in the two titration studies, 61%-82% of the patients treated with lanthanum carbonate had their serum phosphate levels controlled compared with 24-31% of the patients treated with placebo. The mean phosphate levels were 0.45 mmol/L (1.4 mg/dL) to 0.6 mmol/L (1.9 mg/dL) lower with Fosrenol, compared with placebo.

The active comparator study demonstrated that serum phosphate levels were reduced to target levels of 1.8 mmol/l at the end of the 5 week titration period, in 51% of the lanthanum group compared with 57% of the calcium carbonate group. At week 25 the percentage of randomized patients showing

controlled serum phosphate levels was similar in the two treatment groups, 29% on lanthanum and 30% on calcium carbonate (using a missing=failure approach). Mean serum phosphate levels were reduced by a similar amount in both treatment groups.

Further long-term extension studies have demonstrated maintenance of phosphate reduction for some patients following continued administration of at least 2 years of lanthanum carbonate.

Hypercalcaemia was reported in 0.4% of patients with Fosrenol compared with 20.2% on calcium-based binders in comparative studies. Serum PTH concentrations may fluctuate depending on a patient's serum calcium, phosphate and vitamin D status. Fosrenol has not been shown to have any direct effects on serum PTH concentrations.

Changed in histological and histomorphometric parameters were evaluated for 63 paired bone biopsies, at baseline and 1 year, obtained from dialysis patients receiving treatment with Fosrenol or calcium in one clinical study. The results showed that there was no progression to low bone turnover states during the 12 months in those patients treated with Fosrenol. The 12 months bone study also showed that the median lanthanum concentration in bone biopsies taken from lanthanum carbonate hydrate-treated renal dialysis patients rose form 0.3 µg/g at baseline to 1.8 µg/g tissue (wet weight) after one year of treatment (range 0.12-5.51 µg/g). These patients had been treated with 500 to 3750 mg lanthanum/day for up to 1 year. A change from 0.03 µg/g at baseline to 0.06 µg/g tissue (wet weight) after one year treatment (range 0.17-1.0 µg/g) was observed in the group treated with calcium containing phosphate binders.

Paediatric population
An open label study was conducted to investigate the efficacy and safety of Fosrenol in hyperphosphataemic paediatric patients with chronic kidney disease on dialysis. This study did not reach the originally planned sample size required for statistical non inferiority comparison to calcium carbonate, thus only descriptive analysis was performed on the final data. Among the 52 patients in the FAS population, who were exposed to Fosrenol in Parts 2b and 3 combined. 51 enrolled and 10 discontinued in Part 2b; 42 patients enrolled and 7 discontinued in Part 3; the total exposure was 26.4 patient-years; and the observation time was 36.8 patient-years.
After 8 weeks of treatment with Fosrenol, 35% of the subjects included in the primary analysis population met the Kidney Disease Outcome Quality Initiative (KDOQI) specified serum phosphorus target levels (ie. < 1.94 mmol/L for age <12 years; < 1.78 mmol/L for age between 12 and 18 years).
No new significant safety issues with Fosrenol were identified in this study in paediatric subjects with chronic kidney disease who were on dialysis, administered mean daily dose of 1,705 mg (median 1,500 mg).

5.2 Pharmacokinetic properties

As binding between lanthanum and dietary phosphorus occurs in the lumen of the stomach and upper small intestine, the therapeutic effectiveness of Fosrenol is not dependent on levels of lanthanum in the plasma.

Lanthanum is present in the environment. Measurement of background levels in non-lanthanum carbonate hydrate-treated chronic renal failure patients during Phase III clinical trials revealed concentrations of <0.05 to 0.90 ng/mL in plasma, and <0.006 to 1.0 µg/g in bone biopsy samples.

Absorption

Lanthanum carbonate hydrate has low aqueous solubility (<0.01 mg/mL at pH 7.5) and is minimally absorbed following oral administration. Absolute oral bioavailability is estimated to be <0.002% in humans.

In health subjects, plasma AUC and C_{max} increased as a function of dose, but in a less than proportional manner, after single oral doses of 250 to 1000 mg lanthanum, consistent with dissolution-limited absorption. The apparent plasma elimination half-life in healthy subjects was 36 hours.

In renal dialysis patients dosed for 10 days with 1000 mg lanthanum 3 times daily, the mean (± sd) peak plasma concentration was 1.06 (±1.04) ng/mL, and mean AUC_{last} was 31.1 (±40.5) ng.h/mL. Regular blood level monitoring in 1707 renal dialysis patients taking lanthanum carbonate hydrate for up to 2 years showed no increase in plasma lanthanum concentrations over this time period.

Distribution

Lanthanum does not accumulate in plasma in patients or in animals after repeated oral administration of lanthanum carbonate hydrate. The small fraction of orally administered lanthanum absorbed is extensively bound to plasma proteins (>99.7%) and in animal studies, was widely distributed to systemic tissues, predominantly bone, liver and the gastrointestinal tract, including the mesenteric lymph nodes. In long-term animal studies, lanthanum concentrations in several tissues, including the gastrointestinal tract, bone and liver increased over time to levels several orders of magnitude above those in plasma. An apparent steady-state level of lanthanum was attained in some tissues, e.g. the liver whereas levels in gastrointestinal tract increased with duration of treatment. Changes in tissue lanthanum levels after withdrawal of treatment varied between tissues. A relatively high proportion of lanthanum was retained in tissues for longer than 6 months after cessation of dosing (median % retained in bone ≤100% (rat) and ≤87% (dog), and in the liver ≤6% (rat) and ≤82% (dog)).

The mean lanthanum C_{max} and AUC_{last} in children (<12 years) receiving a single 500 mg dose of lanthanum carbonate were approximately one third of the value of those in adolescents (≥12 years) receiving 1000 mg lanthanum carbonate (mean Cmax 0.214 ng/mL vs. 0.646 ng/mL, and mean AUClast 2.57 ng·h/mL vs. 8.31 ng·h/mL, respectively).

In 105 bone biopsies from patients treated with lanthanum for up to 4.5 years, rising levels of lanthanum were noted overtime. Cases of lanthanum deposition in gastrointestinal mucosa, mainly after long term use, have been reported. The clinical significance of this is yet unknown.

No adverse effects were associated with the tissue deposition of lanthanum seen in long-term animal studies with high oral doses of lanthanum carbonate (See Preclinical safety data). (See pharmacodynamic properties for information regarding changes in lanthanum concentrations in bone biopsies taken from renal dialysis patients after one year of treatment with lanthanum containing versus calcium containing phosphate binders).

Metabolism

Lanthanum is not metabolized.

Studies in chronic renal failure patients with hepatic impairment have not been conducted. In patients with co-existing hepatic disorders at the time of entry into Phase III clinical studies, there was no

evidence of increased plasma exposure to lanthanum or worsening hepatic function after treatment with Fosrenol for periods up to 2 years.

Elimination

Lanthanum is excreted mainly in the faeces with only around 0.000031% of an oral dose excreted via the urine in healthy subjects (renal clearance approximately 1mL/min, representing <2% of total plasma clearance).

After intravenous administration to animals, lanthanum is excreted mainly in the faeces (74% of the dose), both via the bile and direct transfer across the gut wall. Renal excretion was a minor route.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Reproductive toxicology

In mouse and rat carcinogenicity studies, lanthanum carbonate had no effect on tumor incidences at dosages up to 1500 mg(salt)kg/day. In mice, a small increase in the incidence of benign gastric adenomas occurred at 1500 mg(salt)/kg/day). The adenomas and associated non-neoplastic pathology were consistent with an adaptive response of the glandular stomach to an altered gastric environment caused by the repeated gavage of large volumes of lanthanum carbonate suspension.

Lanthanum carbonate tested negative for mutagenic activity in an in vitro Ames assay using Salmonella typhimurium and Escherichia coli strains and in vitro HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2,000 mg/kg, and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg.

Lanthanum carbonate hydrate reduced gastric acidity in the rat in a safety pharmacology study.

Reproductive toxicity study in rats administered high doses of lanthanum from day 6 of gestation to day 20 post partum showed that there were no maternal effects, but reduced pup weight and delays in some developmental markers (eye and vaginal opening) were seen. In rabbits given high daily doses of lanthanum during gestation, maternal toxicity with reduced maternal food intake and body weight gain, increased pre- and post- implantation losses and decreased pup weight were seen.

Lanthanum carbonate hydrate was not carcinogenic in mice or rats. In mice, an increase in gastric glandular adenomas was seen in the high-dose group (1500 mg/kg/day). The neoplastic response in the mouse is considered to be related to an exacerbation of spontaneous pathological stomach changes and to be of little clinical significance.

Animal toxicology and/or pharmacology

Non-clinical data revealed no specific hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity, genotoxicity, or fertility.

Studies in animals have shown deposition of lanthanum in tissues, mainly the gastrointestinal tract, mesenteric lymph nodes, liver and bone (see **"Pharmacokinetic properties"**). However, life-time studies in healthy animals do not indicate a hazard for man from the use of Fosrenol. Specific immunotoxicity studies have not been performed..

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrates (hydrated)

Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Keep container tightly closed.

6.5 Nature and content of container

White cylindrical HDPE bottles containing a rayon coil fitted with a tamper evident, child resistant polypropylene screw cap.

Pack sizes

250 mg tablets: 40, 90, 200, 400 tablets. Not all pack sizes may be marketed.

500 mg tablets: 20, 45, 90, 100, 200 tablets. Not all pack sizes may be marketed.

750 mg tablets: 15, 30, 45, 75, 90, 150 tablets. Not all pack sizes may be marketed.

1000 mg tablets: 10, 15, 30, 50, 90, 100 tablets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

7. MANUFACTURED BY

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