Size: 1 18 X 175 mm

For the use of a registered medical practitioner or a hospital or a laboratory only

Lanthanum Carbonate Chewable Tablets

FOSBAIT®

Panacea Biotec

Innovation in support of life

Description
Lanthanum carbonate 500 mg and 250 mg tablets are white to off white uncoated rectangular shaped tablets debossed with FOSBAIT ® on one side and 500/250 on other side.
Composition
FOSBAIT-500
Each uncoated chewable tablet contains:
Lanthanum carbonate equivalent to
Elemental lanthanum.....500 mg
FOSBAIT-250
Each uncoated chewable tablet contains:
Lanthanum carbonate equivalent to
Elemental lanthanum.....250mg
Dosage Form/s
Chewable tablet
Indications
FOSBAIT ® is indicated for the treatment of hyperphosphatemia in patient with end stage renal disease who requires dialysis treatment.
Dose and Method of Administration
Lanthanum Carbonate is for oral administration.
The tablets must be chewed completely and not swallowed whole. To aid with chewing the tablets may be crushed.
Adults, including elderly (> 65 years)
Lanthanum Carbonate should be taken with or immediately after food, with the daily dose divided between meals. Patients should adhere to recommended diets in order to control phosphate and fluid intake. Lanthanum Carbonate is presented as a chewable tablet therefore avoiding the need to take additional fluid. Serum phosphate levels should be monitored and the dose of Lanthanum Carbonate titrated every 2-3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter.
Control of serum phosphate level has been demonstrated at doses starting from 750 mg per day. The maximum dose studied in clinical trials, in a limited number of patients, is 3750mg. Patients who respond to lanthanum therapy; usually achieve acceptable serum phosphate levels at doses of 1500 – 3000 mg lanthanum per day.
Pediatric population
The safety and efficacy of Lanthanum Carbonate in children and adolescents below the age of 18 years has not been established.
Hepatic impairment
The effect of hepatic impairment on Lanthanum Carbonate 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.
Use in special populations
Pregnancy
There are no adequate data from the use of Lanthanum carbonate in pregnant women. Lanthanum carbonate is not recommended for use during pregnancy.
Breast-feeding
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 Lanthanum carbonate, taking into account the potential benefit of breast feeding to the child and the potential benefit of Lanthanum carbonate therapy to the nursing mother.
Fertility
There is no fertility data available on lanthanum carbonate in humans. In rat toxicology studies, lanthanum carbonate had no adverse effects on fertility.
Contraindications
- Hypersensitivity.
- Hypophosphatemia

Warnings and special Precautions
Tissue deposition of Lanthanum has been shown with Lanthanum Carbonate in animal studies. In 105 bone biopsies from patients treated with Lanthanum Carbonate, some for up to 4.5 years, rising levels of lanthanum were noted over time. No clinical data are available on deposition of lanthanum in other human tissues. The use of Lanthanum Carbonate in clinical studies beyond 2 years is currently limited. However, treatment of subjects with Lanthanum Carbonate for up to 6 years has not demonstrated a change in the benefit/risk profile.
Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in clinical studies with Lanthanum Carbonate. Lanthanum Carbonate should be used in these patients following careful assessment of benefit and risk. Lanthanum Carbonate is known to cause constipation and therefore caution should be exercised in patients predisposed to bowel obstruction (e.g. previous abdominal surgery, peritonitis).
Patients with renal insufficiency may develop hypocalcaemia. Lanthanum Carbonate does not contain calcium. Serum calcium levels should therefore be monitored at regular time intervals for this patient population and appropriate supplements given.
Lanthanum is not metabolized by liver enzymes but it is most likely excreted in the bile. 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 .As the liver is the principal organ of elimination of absorbed lanthanum monitoring of liver function tests is recommended.
Safety and efficacy of Lanthanum Carbonate have not been established in children and adolescents; use in children and adolescents is not recommended.
Lanthanum Carbonate should be discontinued if hypophosphatemia develops.
Abdominal x-rays of patients taking Lanthanum Carbonate may have a radio-opaque appearance typical of an imaging agent.
Patients with rare glucose-galactose absorption should not take this medicine.
Drug interactions
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 Lanthanum carbonate (e.g. chloroquine, hydroxychloroquine and ketoconazole).
In healthy subjects, the absorption and pharmacokinetics of lanthanum were not affected by co-administration of citrate.
Serum levels of fat-soluble vitamins A, D, E and K, were not affected by Lanthanum Carbonate administration in clinical studies.
Human volunteer studies have shown that co-administration of Lanthanum Carbonate with digoxin, warfarin or metoprolol does not produce clinically-relevant changes in the pharmacokinetic profiles of these drugs.
In simulated gastric juice, lanthanum carbonate hydrate did not form insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol or enalapril, suggesting a low potential to affect the absorption of these drugs.
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 Lanthanum Carbonate.
The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken with Lanthanum Carbonate in a single dose study in healthy volunteers. It is recommended that oral floxacin formulations are taken at least 2 hours before or 4 hours after Lanthanum Carbonate.
Phosphate binders (including Lanthanum Carbonate) have been shown to reduce the absorption of levothyroxine. Consequently, thyroid hormone replacement therapy should not be taken within 2 hours of dosing with Lanthanum Carbonate and closer monitoring of TSH levels is recommended in patients receiving both medicinal products.
Lanthanum carbonate hydrate is not a substrate for cytochrome P450 and does not significantly inhibit the activities of the major human cytochrome P450 isoenzymes, CYP1A2, CYP2D6, CYP3A4, CYP2C9 or CYP2C19 in vitro.
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 Lanthanum Carbonate with food and generally abated with time with continued dosing. 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	Gastroenteritis, laryngitis
Blood and lymphatic system disorders	
Uncommon	Eosinophilia
Endocrine disorders	
Uncommon	Hyperparathyroidism
Metabolism and nutrition disorders	
Common	Hypocalcaemia
Uncommon	Hypercalcaemia, hyperglycaemia, hyperphosphataemia, hypophosphataemia, anorexia, appetite increased
Nervous system disorders	
Very Common	Headache
Uncommon	Dizziness, taste alteration

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Ear and Labyrinth disorders	
Uncommon	Vertigo
Gastrointestinal disorders	
Very Common	Abdominal pain, diarrhoea, nausea, vomiting
Common	Constipation, dyspepsia, flatulence
Uncommon	Ileus, subileus, intestinal obstruction, irritable bowel syndrome, oesophagitis, stomatitis, loose stools, indigestion, gastrointestinal disorder (not otherwise specified), dry mouth, tooth disorder, eructation
Rare	Intestinal perforation
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, sweating increased
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia, myalgia, osteoporosis
General disorders and administration site conditions	
Uncommon	Asthenia, chest pain, fatigue, malaise, peripheral oedema, pain, thirst
Investigations	
Uncommon	Blood aluminium increased, increase in GGT, increases in hepatic transaminases, alkaline phosphatase increased, weight decrease

Post marketing experience: During post-approval use of Lanthanum carbonate, cases of allergic skin reactions (including skin rashes, urticaria 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 Lanthanum carbonate 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.

Overdose

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

Pharmacodynamics and Pharmacokinetic Properties

Pharmacodynamics Properties;

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia. ATC code: V03AE03
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 hemodialysis 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.
Two placebo-controlled, randomized studies enrolled patients on dialysis after a washout from previous phosphate binders. After titration of lanthanum carbonate to achieve a serum phosphate level between 1.3 and 1.8mmol/L in one study (doses up to 2250mg/day), or ≤1.8mmol/L in a second study (doses up to 3000mg/day), patients were randomized to lanthanum carbonate or placebo as maintenance treatment. After the 4-week randomized placebo-controlled phase, the serum phosphate concentration rose between 0.5 and 0.6mmol/L in the placebo group, in both studies, relative to patients who remained on lanthanum carbonate therapy. There were 61% patients on lanthanum carbonate who maintained their response, compared to 23% on placebo.
The active comparator study demonstrated that serum phosphate levels were reduced to target levels of 1.8mmol/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.
Hypocalcaemia was reported in 0.4% of patients with Lanthanum Carbonate 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. Lanthanum Carbonate has not been shown to have any direct ef fects on serum PTH concentratrions.
In the long-term bone studies a trend towards increasing bone lanthanum concentrations with time in the control population was observed from the averaged data, the median rising 3-fold from a baseline of 53 µg/kg at 24 months. In patients treated with lanthanum carbonate, the bone lanthanum concentration increased during the first 12 months of lanthanum carbonate treatment up to a median of 1328µg/kg (range 122-5513µg/kg). Median and range concentrations at 18 and 24 months were similar to 12 months. The median at 54 months was 4246µg/kg (range 1673-9792µg/kg).
Paired bone biopsies (at baseline and at one or two years) in patients randomized to either Lanthanum Carbonate or calcium carbonate in one study and patients randomized to either Lanthanum Carbonate or alternative therapy in a second study, showed no differences in the development of mineralization defects between the groups.

Pediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with in Lanthanum Carbonate one or more subsets of the paediatric population in treatment of hyperphosphatemia.

Pharmacokinetic properties

As binding between lanthanum and dietary phosphorus occurs in the lumen of the stomach and upper small intestine, the therapeutic effectiveness of lanthanum carbonate 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 healthy subjects, plasma AUC and Cmax 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). 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 5.3) (See section 5.1 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 lanthanum carbonate for periods up to 2 years.

Elimination

Lanthanum is excreted mainly in the faces 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 faces (74% of the dose), both via the bile and direct transfer across the gut wall. Renal excretion was a minor route.

Incompatibilities: Not known
Shelf-life: Do not use the product after expiry date, printed on container label.
Packaging Information
FOSBAIT® 500/250 supplied as a chewable tablet in bottle of 30s.
Storage and handling instructions
Store at a temperature below 25°C, protect from light and moisture.
Keep the bottle tightly closed after opening.

For more information and further detail contact:
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