SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lanthanum 500 mg chewable tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500 mg chewable tablet contains lanthanum carbonate octahydrate equivalent to 500 mg lanthanum.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet.

500 mg chewable tablets:
White to off-white, round, flat-faced, bevelled-edge tablet, debossed with 'M' on one side of the tablet and '**LC**' over '**500**' on the other side. Each tablet has approximately 15 mm of diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lanthanum is indicated in adult patients 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).

Lanthanum is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥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

Posology
Lanthanum is for oral administration.

The tablets must be chewed completely and not swallowed whole. To aid with chewing the tablets may be crushed.
Other dosage forms are available in the market for patients who have difficulty chewing the tablets.

Adults, including elderly (> 65 years)
Lanthanum should be taken with food or immediately after, with the daily dose divided between meals. Patients should adhere to recommended diets in order to control phosphate and fluid intake. Lanthanum 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 to 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 3750 mg. Patients who respond to lanthanum therapy, usually achieve acceptable serum phosphate levels at doses of 1500 – 3000 mg lanthanum per day.

Paediatric population
The safety and efficacy of Lanthanum in children and adolescents below the age of 18 years have not been established (see sections 4.8 and 5.1). Current 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 Lanthanum pharmacokinetics has not been assessed. Due to its mechanism of action and the lack of liver metabolism doses in patients with hepatic impairment should not be modified, but patients should be monitored carefully (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypophosphataemia.

Bowel obstruction.

4.4 Special warnings and precautions for use

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 (see section 5.1). Cases of lanthanum deposition in gastrointestinal mucosa, mainly after long term use, have been reported. 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.

Data on 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.

There have been cases of gastrointestinal obstruction, ileus, subileus, and gastrointestinal perforation reported in association with lanthanum, some requiring surgery or hospitalisation (see section 4.8).

Lanthanum treatment in 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 in subjects with medications known to potentiate these effects, should only be used after careful consideration. In subjects with ongoing bowel obstruction, lanthanum treatment is contraindicated (see section 4.3).

For all subjects, physicians and patients should remain alert for signs and symptoms of gastrointestinal disorders, especially constipation and abdominal pain/distension which may indicate bowel obstruction, ileus or subileus during treatment with lanthanum carbonate.

Withdrawal of lanthanum carbonate is recommended in patients who develop severe constipation or other severe gastrointestinal signs and symptoms, irrespective of predisposing conditions.

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

Lanthanum tablets must be chewed completely and not swallowed whole (see section 4.2). Serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed Lanthanum tablets.

Patients with renal insufficiency may develop hypocalcaemia. Lanthanum 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 metabolised 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 (see sections 5.2 and 5.3). As the

liver is the principal organ of elimination of absorbed lanthanum monitoring of liver function tests is recommended.

Lanthanum should be discontinued if hypophosphataemia develops.

Abdominal X-rays of patients taking Lanthanum may have a radio-opaque appearance typical of an imaging agent.

4.5 Interaction with other medicinal products and other forms of interaction

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 (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.

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.

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 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*.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of lanthanum carbonate in pregnant women.

One study in rats showed reproductive foetotoxicity (delayed eye opening and sexual maturation) and reduced pup weights at high doses (see section 5.3). The potential risk for humans is unknown.

Lanthanum 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, taking into account the potential benefit of breast feeding to the child and the potential benefit of Lanthanum therapy to the nursing mother.

Fertility

There are no fertility data available on lanthanum carbonate in humans. In rat toxicology studies, lanthanum carbonate had no adverse effects on fertility.

4.7 Effects on ability to drive and use machines

Lanthanum may induce dizziness and vertigo, which may impair the ability to drive and use machines.

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 Lanthanum 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	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
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.
Not known	Product residue present[1]

[1]See Lanthanum deposition in gastrointestinal mucosa warning in section 4.4.

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.

Although there have been a number of additional isolated reactions reported, none of these 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products. Drugs for treatment of hyperkalaemia and hyperphosphatemia, ATC code: V03A E03.

Lanthanum 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.

Two placebo-controlled, randomised 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 1.8 mmol/L in one study (doses up to 2250 mg/day), or ≤1.8 mmol/L in a second study (doses up to 3000 mg/day), patients were randomised to lanthanum carbonate or placebo as maintenance treatment. After the 4-week randomised placebo-controlled phase, the serum phosphate concentration rose between 0.5 and 0.6 mmol/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 1.8 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 randomised 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 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 effects on serum PTH concentrations.

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 1328 μg/kg (range 122-5513 μg/kg). Median and range concentrations at 18 and 24 months were similar to 12 months. The median at 54 months was 4246 μg/kg (range 1673-9792 μg/kg).

Paired bone biopsies (at baseline and at one or two years) in patients randomised to either lanthanum carbonate or calcium carbonate in one study and patients randomised to either lanthanum carbonate or alternative therapy in a second study, showed no differences in the development of mineralization defects between the groups.

Paediatric population
An open-label study was conducted to investigate the efficacy and safety of lanthanum carbonate 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 lanthanum carbonate 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 lanthanum carbonate, 35% of the subjects included in the primary analysis population met the Kidney Disease Outcomes Quality Initiative (KDOQI) specified serum phosphorus target levels (i.e.< 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 lanthanum carbonate were identified in this study in paediatric subjects with chronic kidney disease who were on dialysis, administered mean daily dose of 1705 mg (median 1500 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 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 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). 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 section 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).

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 C_{max} 0.214 ng/mL vs. 0.646 ng/mL, and mean AUC_{last} 2.57 ng·h/mL vs. 8.31 ng·h/mL, respectively).

Biotransformation
Lanthanum is not metabolised.
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 faeces with only around 0.000031% of an oral dose excreted via the urine in healthy subjects (renal clearance approximately 1 mL/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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.
Lanthanum carbonate hydrate reduced gastric acidity in the rat in a safety pharmacology study.

In rats administered high doses of lanthanum carbonate hydrate from day 6 of gestation to day 20 postpartum 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 carbonate hydrate 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.

Studies in animals have shown deposition of lanthanum in tissues, mainly the gastrointestinal tract, mesenteric lymph nodes, liver and bone (see section 5.2). However, life-time studies in healthy animals do not indicate a hazard for man from the use of lanthanum carbonate. Specific immunotoxicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Cellulose microcrystalline & Guar gum
Cellulose microcrystalline
Hydroxypropylcellulose
Silica, colloidal anhydrous
Acesulfame potassium [E950]
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

HDPE bottle with opaque polypropylene screw cap with aluminium induction sealing liner wad and absorbent cotton.

Each 500 mg Lanthanum tablets pack contains 1 bottle with 45 tablets or 2 bottles with 45 tablets each (90 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

Mylan,

Potters Bar,

EN6 1TL,

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1780

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/12/2020

10 DATE OF REVISION OF THE TEXT

28/04/2025