Title: METHOD OF TREATMENT USING LANTHANUM COMPOUNDS

Abstract: This invention relates to a method for treating patients with hypercalcemia, in particular renal failure patients, using lanthanum compounds. The lanthanum compound can be therapeutically administered concurrently to patients receiving other drugs, e.g., digoxin, warfarin or metoprolol, with no adverse consequences.
METHOD OF TREATMENT USING LANTHANUM COMPOUNDS

This application claims priority to U.S. provisional application 60/378,401 (filed May 8, 2002).

BACKGROUND

Hyperphosphataemia is a particular problem of patients with chronic renal failure using dialysis equipment and with about 70% of patients with end stage renal disease (ESRD). This condition can lead to severe bone problems and metastatic calcification of major organs and is associated with significant morbidity and mortality. Conventional dialysis fails to reduce the levels of phosphate in the blood, so that levels rise in time. Elevated phosphate levels are treated using a combination of dietary restrictions and phosphate-binding agents. Phosphate binders chelate phosphate ions and prevent their absorption from the gastrointestinal (GI) tract. Conventional treatments with phosphate binders such as aluminum or calcium salts for the removal of phosphate have serious side effects on the patient. Aluminum-based therapy has known toxic effects (e.g., bone toxicity, haematological disturbances and undesirable effects on the nervous system) and tends to be avoided. Calcium in the form of calcium carbonate is readily absorbed from the gut but may increase the risk of soft-tissue calcification. Moreover, calcium-based treatments can lead to hypercalcemia, which results from the complex elimination kinetics of phosphate during dialysis.

Hypercalcemia is a common occurrence in dialysis patients using calcium-based phosphate binders such as calcium carbonate or calcium acetate. Also, hypercalcemia can result from a multitude of other clinical disorders. The causes are divided into PTH-mediated hypercalcemia and non-PTH mediated hypercalcemia. Hypercalcemia is a fairly common metabolic emergency and patients with cancer often develop hypercalcemia. Hypercalcemia associated with malignancy commonly is the result of breast or lung cancer and is caused by an increased osteoclastic activity within the bone. Symptoms of hypercalcemia
depend on the underlying cause of the disease, the time over which it develops, and the overall physical health of the patient.

Certain forms of lanthanum carbonate have been used to treat bone diseases (WO 02/002277) and for use in treating hyperphosphataemia in patients with renal failure (US 5,968,976). US patent 5,968,976 describes the preparation and use in a pharmaceutical composition of certain hydrates of lanthanum carbonate for the treatment of hyperphosphataemia. WO 02/002277 describes a method for enhancing bone formation in a mammal in need thereof comprising administering to the mammal an effective amount of a lanthanum compound, preferably lanthanum III.

There exists a need for an agent which can be used to treat hypercalcemia in patients suffering from a variety of clinical disorders. In particular, there exists a need to identify a phosphate binder which can be administered to a renal failure patient or a patient with a bone disorder wherein the level of calcium in the serum of the patient can be more easily maintained at homeostasis levels with no or reduced incidences of hypercalcemia.

SUMMARY OF THE INVENTION

This invention relates to a method for controlling hypercalcemia in a patient comprising administering a therapeutically effective amount of a lanthanum compound.

This invention relates to a method for treating hypercalcemia in a patient comprising administering a therapeutically effective amount of a lanthanum compound.
This invention relates to a method for controlling metastatic calcification in a patient comprising administering a therapeutically effective amount of a lanthanum compound.

This invention relates to a method for treating metastatic calcification in a patient comprising administering a therapeutically effective amount of a lanthanum compound.

In one embodiment, the invention relates to a method for treating a patient with hypercalcemia comprising administering a therapeutically effective amount of lanthanum carbonate and wherein said patient is being concomitantly treated with a drug for another clinical disorder.

In another embodiment, the invention relates to a method for treating a patient with metastatic calcification comprising administering a therapeutically effective amount of lanthanum carbonate and wherein said patient is being concomitantly treated with a drug for another clinical disorder.

In one embodiment, the invention relates to a method for treating hypercalcemia in renal failure patients, including but not limited to patients receiving dialysis and patients with end-stage renal disease (ESRD), comprising administering a therapeutically effective amount of a lanthanum compound.

In one embodiment, the invention relates to a method for treating metastatic calcification in renal failure patients, including but not limited to patients receiving dialysis and patients with end-stage renal disease (ESRD), comprising administering a therapeutically effective amount of a lanthanum compound.

In a preferred embodiment, the invention relates to a method for treating a patient with hypercalcemia comprising administering a therapeutically effective
amount of a lanthanum compound and wherein said patient is being concomitantly treated with digoxin.

In another preferred embodiment, the invention relates to a method for treating a patient with hypercalcemia comprising administering a therapeutically effective amount a lanthanum compound and wherein said patient is being concomitantly treated with warfarin.

In another preferred embodiment, the invention relates to a method for treating a patient with hypercalcemia comprising administering a therapeutically effective amount a lanthanum compound and wherein said patient is being concomitantly treated with metoprolol.

This invention further relates to combinations (formulated or in vivo) of the lanthanum compounds of this invention with such other drugs.

This invention relates to a method for treating hypercalcemia in a patient, in particular patients on renal dialysis. This invention further relates to a method for treating hypercalcemic patients who are concurrently being treated with drugs for other clinical disorders, such as e.g., cardiovascular ailments. The lanthanum carbonate can be administered concurrently with other drugs, for such ailments and others, with no or minimal adverse consequences, e.g. drug-drug interactions.

This invention relates to a method for treating metastatic calcification in a patient, in particular patients on renal dialysis. This invention further relates to a method for treating metastatic calcification patients who are concurrently being treated with drugs for other clinical disorders, such as e.g., cardiovascular ailments. The lanthanum compound can be administered concurrently with other drugs, for such ailments and others, with no or minimal adverse consequences, e.g. drug-drug interactions.
In another embodiment of the invention, the lanthanum carbonate compound can be administered to a patient with hypercalcemia, metastatic calcification or renal failure simultaneously with digoxin, warfarin or metoprolol in the same formulation, or more typically in separate formulations, and often using different administration routes. Administration can also be sequentially, in any order, and in time periods sufficient to make the administered agents bioavailable concurrently or within therapeutically effective times.

In another embodiment, the lanthanum carbonate can be administered in tandem with digoxin or warfarin or metoprolol to a patient, wherein the digoxin or warfarin or metoprolol can be administered to a patient after administration of the lanthanum to said patient.

The term “hypercalcemia” as used herein represents an abnormally high concentration of calcium compounds in the circulating blood.

The term “metastatic calcification” as used herein represents the deposit of calcereous material in remote tissues.

Lanthanum is a rare earth element with an atomic number of 57. The properties of lanthanum make this agent a good candidate as a useful phosphate binder. It has a high affinity for binding phosphorus and in the form of its carbonate salt, has a low solubility that limits gastrointestinal absorption. In addition, the phosphate binding is independent of pH, it possesses a low toxic potential based on the LD₅₀, it is palatable, abundant, and has limited effects on serum electrolyte concentrations (Hutchison, AJ et al. (1998) Perit. Dial. Int. 18(Suppl 2): S38.

The term "lanthanum compound" is used herein to denote any pharmacologically acceptable lanthanum compound capable of ensuring that the lanthanum is bioavailable. Preferred compounds include, for example, lanthanum
salts and derivatives thereof, lanthanum resins and lanthanum absorbants. The lanthanum may if desired be in the form of a chelate.

Preferred lanthanum compound include lanthanum carbonate compounds. Lanthanum carbonate compounds refers to all forms of lanthanum carbonate.

In particular, the invention relates to lanthanum carbonate of the general formula:

$$\text{La}_2(\text{CO}_3)_3 \times \text{H}_2\text{O}$$

where x has a value from 3 to 6, preferably from 3.5 to 5, more preferably from 3.8 to 4.5, for the preparation of a medicament for the treatment of hypercalcemia by administration into the gastrointestinal tract, see e.g., U.S. Patent No. 5,968,976 which is incorporated herein by reference.

The lanthanum compounds of the invention may be administered in the form of a pharmaceutical composition comprising the active ingredient in admixture or association with a pharmaceutically acceptable carrier or diluent. The active ingredient may be formulated into a composition suitable for administration by any convenient route, e.g. orally (including sublingually), topically, parenterally (including intravenous, intramuscular, intraperitoneal and subcutaneous administration) and rectally, oral administration being preferred. It should be understood, however, that the invention embraces all forms of administration which make the lanthanum systemically or locally available.

Orally administrable compositions may, if desired, contain one or more physiologically compatible carriers and/or excipients and may be solid or liquid. The compositions may take any convenient form including, for example, tablets, coated tablets, capsules, lozenges, aqueous or oily suspensions, solutions, emulsions, syrups, elixirs and dry products suitable for reconstitution with water or another suitable liquid vehicle before use. The compositions may advantageously be prepared in dosage unit form. Tablets and capsules according
to the invention may, if desired, contain conventional ingredients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. Tablets may be coated according to methods well known in the art.

Liquid compositions may contain conventional additives such as suspending agents, for example sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles, which may include edible oils, for example vegetable oils such as arachis oil, almond oil, fractionated coconut oil, fish-liver oils, oily esters such as polysorbate 80, propylene glycol, or ethyl alcohol; and preservatives, for example methyl or propyl p-hydroxybenzoates or sorbic acid. Liquid compositions may conveniently be encapsulated in, for example, gelatin to give a product in dosage unit form.

Formulations for oral delivery may be formulated in a delayed release formulation such that the lanthanum is delivered to the large intestine. This will lessen the interaction of lanthanum with dietary phosphate which results in the precipitation of lanthanum phosphate, which is poorly absorbed by the gut. Delayed release formulations are well known in the art and include for example, delayed release capsules or time pills, osmotic delivery capsules etc.

Compositions for parenteral administration may be formulated using an injectable liquid carrier such as sterile pyrogen-free water, sterile peroxide-free ethyl oleate, dehydrated alcohol or propylene glycol or a dehydrated alcohol/propylene glycol mixture, and may be injected intravenously, intraperitoneally, subcutaneously or intramuscularly.
Compositions for rectal administration may be formulated using a conventional suppository base such as cocoa butter or another glyceride.

Compositions for topical administration include ointments, creams, gels, lotions, shampoos, paints, powders (including spray powders), pessaries, tampons, sprays, dips, aerosols, pour-ons and drops. The active ingredient may, for example, be formulated in a hydrophilic or hydrophobic base as appropriate.

It may be advantageous to incorporate an antioxidant, for example ascorbic acid, butylated hydroxyanisole or hydroquinone in the compositions of the invention to enhance their storage life.

Administration in this invention may consist of one or more cycles; during these cycles one or more periods of osteoclastic and osteoblastic activity will occur, as well as one or more periods when there is neither osteoclastic nor osteoblastic activity.

Alternatively, administration may be conducted in an uninterrupted regimen; such a regimen may be a long term regimen, e.g. a permanent regimen.

It will be understood that the dosages of compositions and the duration of administration according to the invention will vary depending on the requirements of the particular subject. The precise dosage regime will be determined by the attending physician or veterinary surgeon who will, inter alia, consider factors such as body weight, age and symptoms (if any). The compositions may if desired incorporate one or more further active ingredients.

During the dosing regimen, administration may be effected once or more times per day, for example once, twice, three or four times per day.
The invention further provides a pharmaceutical composition comprising the lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration for the treatment of hypercalcemia.

The lanthanum carbonate can be administered in a conventional formulation or regimen as is routinely done.

It will be appreciated by those of skill in the art that the particular method of administration will depend on a variety of factors, all of which are routinely considered when administering therapeutics. It will also be understood, however, that the specific dose level for any patient will depend upon a variety of factors, including the activity of the specific compounds employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, the time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition (hypercalcemia) undergoing treatment.

It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of dosages and dosage given for a defined number of days can be ascertained by those skilled in the art using conventional treatment tests.

The usefulness of administering lanthanum carbonate to a patient receiving another drug as for example digoxin or warfarin is better than could have been expected from conventional knowledge of the potentially adverse drug-drug interactions often observed with such chemically distinct compounds.

The lanthanum carbonate compound can be administered in tandem with other drugs which are used to treat a variety of clinical disorders including but not limited to cardiovascular ailments. The lanthanum carbonate compound can be
administered once per day for several consecutive days followed by administration of the other drug. Also, the other drug, as for example digoxin or warfarin, can be administered first followed by lanthanum carbonate. Also, the other administered agent can be administered using any regimen which is conventionally used for the agent.

Any of the routes and regimens of administration may be modified depending on any superior or unexpected results which may be obtained as routinely determined with this invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilized the present invention to its fullest extent. The following preferred embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLES

Example 1

A study was conducted to evaluate the incidence of hypercalcemic episodes in dialysis patients being treated with lanthanum carbonate versus patients being treated with calcium carbonate.
Hypercalcemia is a common occurrence in dialysis patients and is associated with an increase in morbidity. The reduction or elimination of such episodes in dialysis patients who have serious underlying disease is a potentially significant advantage of lanthanum treatment. A summary of the occurrence of hypercalcemic episodes (i.e. serum calcium above ULN i.e. > 2.65 mmol/L [> 10.6 mg/dL]) in the ITT population (intent-to-treat population) during the study is shown in Table 1. In total, 6% of patients in the lanthanum group and 48% of patients in the calcium carbonate group had at least one hypercalcemic episode. The substantially greater incidence in the calcium carbonate group was predictable and likely to be a result of greater calcium burden in these patients. The number of hypercalcemic episodes for the lanthanum group was low.

Table 1. Number of hypercalcemic episodes (ITT population)

<table>
<thead>
<tr>
<th>Number of hypercalcemic episodes</th>
<th>Lanthanum Group</th>
<th>Calcium Carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>N (%)</td>
<td>N</td>
</tr>
<tr>
<td>0</td>
<td>46 (94%)</td>
<td>25</td>
</tr>
<tr>
<td>(51%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>2 (4%)</td>
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<tr>
<td>(21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>(8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>(6%)</td>
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<td></td>
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<tr>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>(8%)</td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>(2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Example 2

A study was conducted to assess the affect of lanthanum carbonate on the pharmacokinetics of concomitant treatment with digoxin.

Fourteen healthy volunteers entered this open-label, randomized, two-way crossover study and received either digoxin 0.5 mg on its own or 30 min after a fourth dose of lanthanum carbonate (1 gram of lanthanum, 3 doses given 1 day before digoxin administration). After a 16 day drug-free period, individuals crossed over to receive the other treatment schedule. Pharmacokinetic parameters were determined using non-comparmental methods.

Ninety-percent confidence intervals for maximum serum concentration of digoxin and the area under the serum concentration-time curve from 0 to last observed concentration were within bioequivalence criteria for a log-transformed variable (i.e. 0.80, 1.25), as was the time to maximum serum concentration. Serum half life for digoxin was slightly higher after concomitant treatment with lanthanum carbonate (digoxin vs. digoxin/lanthanum carbonate: 11.4 ± 15.7 h vs. 14.8 ± 19.0 h), and 90% confidence intervals for this parameter and the terminal phase elimination rate constant were outside the bioequivalence criteria. However, these differences were small and not considered clinically significant. Only 4 adverse events occurred (2 after treatment with digoxin alone and 2 after concomitant treatment with lanthanum carbonate), one of which were severe or thought likely to be related to treatment.

The results show that lanthanum carbonate has little effect on the pharmacokinetics of concomitant digoxin treatment, allowing the agents to be taken concomitantly without any special precaution other than those usually required.
Example 3

Study to assess the affect of lanthanum carbonate on the pharmacokinetics of concomitant treatment with warfarin.

Fourteen healthy volunteers received either warfarin 10 mg or warfarin 10 mg 30 minutes after a fourth dose (3 doses given 1 day before warfarin administration) of 1 gram of lanthanum carbonate. After a period of 16 days, individuals crossed over to receive the other treatment schedule. Pharmacokinetic parameters were determined using concomparmental methods.

The 90% confidence intervals for all of the pharmacokinetic parameters measured (e.g. maximum plasma concentration, area under the plasma concentration-time curve from time 0 to infinity, time to maximum concentration, plasma half-life) were well within the bioequivalence criteria for a log transformed variable (i.e. 0.80, 1.25). No serious adverse events occurred. Only 5 adverse events were reported and these were all considered to be not related or unlikely to be related to study agents.

The results show that lanthanum carbonate has no effect on the pharmacokinetics of concomitant warfarin treatment, allowing the agents to be taken concomitantly without any special precaution other than those usually required.

Example 4
Lanthanum Carbonate has no Clinically Significant Effect on the Pharmacokinetics of Digoxin, Warfarin or Metoprolol

Lanthanum carbonate (LC) is a novel phosphate binder for the treatment of hyperphosphataemia in patients with end-stage renal disease. In clinical practice, these patients often receive numerous concomitant medications. Warfarin and digoxin are drugs with a narrow therapeutic range and were thus
selected for investigation in this study. Metoprolol was also investigated as it represents a common acidic drug with which there is potential for interaction in the gastrointestinal tract.

Methods

Fourteen healthy men were enrolled into each of three open-label, randomized, cross-over studies. In Study 1, each volunteer received warfarin 10 mg on its own or 30 minutes after a fourth dose of LC 1000 mg (3 doses given 1 day before warfarin treatment). After 16 drug-free days, volunteers crossed over to the other treatment schedule. In Studies 2 and 3, participants received metoprolol 100 mg and digoxin 0.5 mg, respectively. In Study 2, the washout phase between treatment schedules was 8 days. Pharmacokinetic parameters \( (C_{\text{max}}, \text{AUC}_0-\infty, \text{AUC}_{\text{last}}, T_{\text{max}}, t_{1/2}) \) were assessed using non-compartmental methods.

Results

For warfarin, bioequivalence criteria were met for all parameters. With metoprolol, bioequivalence criteria were met for \( \text{AUC}_0-\infty, \text{AUC}_{\text{last}}, T_{\text{max}}, t_{1/2} \) and the terminal phase rate-elimination constant. The 90% confidence intervals for metoprolol \( C_{\text{max}} \) were slightly outside bioequivalence criteria, but the difference was not considered to be clinically relevant. All parameters for digoxin except \( t_{1/2} \) met bioequivalence criteria. The data suggest, however, that the rate and extent of absorption of digoxin are not influenced by LC. All treatments were well tolerated, with no serious adverse events.

Co-administration of LC has little effect on the pharmacokinetics of warfarin, metoprolol or digoxin. Thus, no additional precautions are required when these medications are administered concomitantly.
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of the invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
WHAT IS CLAIMED IS:

1. A method for controlling hypercalcemia or metastatic calcification in a patient comprising administering a therapeutically effective amount of a lanthanum compound.

2. A method for treating hypercalcemia or metastatic calcification in a patient comprising administering a therapeutically effective amount of a lanthanum compound.

3. The method of claim 2, wherein said patient is being concomitantly treated with a drug for another clinical disorder.

4. The method of claim 3, wherein said lanthanum compound is a lanthanum carbonate.

5. The method of claim 4, wherein said drug is digoxin, warfarin or metoprolol.

6. The method of claim 4, wherein said disorder is a cardiovascular disorder.

7. The method of claim 4, wherein said lanthanum carbonate is administered before, after or during the administration of said drug with no or a minimal adverse interaction.

8. The method of claim 5, wherein said digoxin, warfarin or metoprolol is administered to said patient after the administration of said lanthanum.

9. A method for treating hypercalcemia or metastatic calcification in a renal failure patient, a patient receiving dialysis or a patient with end-stage renal disease
comprising administering a therapeutically effective amount of a lanthanum compound.

10. A method for treating hyperphosphatemia and another disease affecting a chronic renal failure patient comprising administering an effective amount of a first agent for treating said another disease and an effective amount of a lanthanum compound for treating hyperphosphatemia without an adverse interaction with said first agent.

11. The method of claim 10, wherein said another disease is a cardiovascular disorder.

12. The method of claim 10, wherein said first agent is digoxin, warfarin or metoprolol.

13. The method of claim 10, wherein said lanthanum compound is a lanthanum carbonate.


15. The method of claim 4, wherein said lanthanum carbonate has the general formula

\[ \text{La}_2(\text{CO}_3)_3 \cdot x \cdot \text{H}_2\text{O} \]

wherein x has a value ranging from 3 to 6.

16. The method of claim 15, wherein x has a value ranging from 3.5 to 5.

17. The method of claim 16, wherein x has a value ranging from 3.8 to 4.5.
18. Use of a lanthanum compound in the manufacture of a medicament for controlling hypercalcemia or metastatic calcification in a patient.

19. Use of a lanthanum compound in the manufacture of a medicament for treating hypercalcemia or metastatic calcification in a patient.

20. Use of claim 18 or 19, wherein said lanthanum compound is a lanthanum carbonate.

21. Use of claim 19, wherein said patient is being concomitantly treated with digoxin, warfarin or metoprolol.

22. Use of claim 21, wherein said digoxin, warfarin or metoprolol is adapted to be administered to said patient after the administration of said lanthanum.

23. A lanthanum compound for use in treating hypercalcemia or metastatic calcification in a renal failure patient, a patient receiving dialysis or a patient with end-stage renal disease.

24. Use of a lanthanum compound in the manufacture of a medicament for treating hyperphosphatemia, in conjunction with an agent for treating another disease affecting a chronic renal failure patient, without an adverse interaction of said medicament with said agent.

25. Use of claim 24, wherein said another disease is a cardiovascular disorder.

26. Use of claim 24 or 25, wherein said agent is digoxin, warfarin or metoprolol.

27. Use of claim 24, 25 or 26, wherein said lanthanum compound is a lanthanum carbonate.
28. Use of a lanthanum compound in the manufacture of a medicament for preventing hypercalcemia in a patient.

29. Use of claim 20, wherein said lanthanum carbonate has the general formula

$$\text{La}_2(\text{CO}_3)_3 \cdot x \text{ H}_2\text{O}$$

wherein $x$ has a value ranging from 3 to 6.

30. Use of claim 29, wherein $x$ has a value ranging from 3.5 to 5.

31. Use of claim 30, wherein $x$ has a value ranging from 3.8 to 4.5.