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(54) Benævnelse: **FARMACEUTISKE PRÆPARATER MED ZOLEDRONSYRE, KALCIUM OG D-VITAMIN, EGNEDE TIL BEHANDLING OG/ELLER PROFYLAKSE AF SYGDOMME I KNOGLESTOFSKIFTET OG AF TERAPIBETINGEDE BIVIRKNINGER SÅSOM HYPOKALCÆMIER**

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BOURKE S ET AL: "The impact of dietary calcium intake and vitamin D status on the effects of zoledronate", OSTEOPOROSIS INTERNATIONAL ; WITH OTHER METABOLIC BONE DISEASES, SPRINGER-VERLAG, LO, Bd. 24, Nr. 1, 15. August 2012 (2012-08-15), Seiten 349-354, XP035158420, ISSN: 1433-2965, DOI: 10.1007/S00198-012-2117-4

Description

Technical field

The present invention relates to pharmaceutical compositions comprising zoledronic acid, calcium and vitamin D, which are suitable for the treatment and/or prophylaxis of treatment-related side effects such as hypocalcaemia in diseases related to bone metabolism caused by the effect of zoledronic acid.

Description

The treatment of diseases relates to bone metabolism, such as osteoporosis, tumour diseases including induced bone loss (CTIBL, cancer treatment-induced bone loss), Paget's disease or hypocalcaemia, is an important focus of medical research. Human bone consists of an organic matrix, which is combined with inorganic salts – predominantly calcium and phosphate in the form of hydroxylapatite ($Ca_3(PO_4)_2 \bullet Ca(OH)_2$). As a basic principle, bone physiology in humans is based on the constant formation and resorption (bone turnover) of bone substance. Bone formation and resorption in the context of continual remodelling is regulated hormonally (substantially by oestrogen, parathormone (PTH)) and by signal transduction pathways (substantially RANKL (receptor activator of nuclear factor-kB ligand)/OPG (osteoprotegerin) and Ca/PTH/vitamin D3). During childhood and especially puberty, more bone is formed than is resorbed; in old age, in women in particular during and after the menopause, "net" bone resorption increasingly occurs.

In the course of a human lifetime, bone is continually exposed to physiological mechanical loads and adapts accordingly. This was described for the first time by Julius Wolff in 1862, and Wolff's law forms the basis for the biomechanical understanding of bone. Wolff was able to show, when studying femoral heads, that bone adapts in its form to the function and degenerates if it is permanently not loaded. Thus, as part of remodelling, bone that is not loaded is resorbed, which was investigated in the

bed-rest studies with absolute bed rest over a period of 60 days. Bone that is subjected to high mechanical loads, on the other hand, is strengthened according to the lines of force, which could be shown, for example, in the lower arm bones of tennis players.

In addition to regular remodelling processes, the action of force on bone leads to microdamage or discontinuities (fractures) with and without defect formation, which can heal without scarring. In inorganic materials, repetitive loading below the fracture limit leads to material fatigue/material fatigue fracture in that small cracks form and grow until they reach a critical size and the material fractures. As a quasi-brittle material, which absorbs energy by the formation of small cracks (so-called micro-cracks), it is able to avoid bone fractures. Micro-cracks were described as early as 1960 by Harold Frost and are clearly delimited cracks having a length of 50-100 µm, which occur predominantly in the interstitial bone. They are generally longer in the longitudinal axis than in the transverse axis, corresponding to the biomechanical loading, form in the trabecular and cortical bone even under physiological, repetitive loading such as walking and running, and occur significantly increasingly in old age.

In bone, micro-cracks generally remain clinically without symptoms since they are continually repaired and healed as part of remodelling. The crack leads to the apoptosis of osteocytes, which release factors, *inter alia* RANKL. These trigger osteoclastic resorption, with subsequent osteoblastic bone formation.

While healthy bone prevents and repairs the progression of microdamage, accumulation and optionally increased fracture susceptibility, for example in the case of atypical femur fractures, can occur in aged bone or where remodelling is suppressed, for example, by highly potent antiresorptive medicaments, for example bisphosphonates or anti-RANKL antibodies.

The rebuilding processes that take place continually in bone as part of remodelling involve substantially osteoblasts, osteoclasts and osteocytes. While osteoclasts resorb bone, osteoblasts can form bone.

Ultimately, the role of the osteocytes has hitherto still not been explained in detail. Osteocytes are terminally differentiated cells of osteoblastic origin which are immured in the bone and are connected together and communicate with one another. If damage occurs to the osteocyte extensions, for example within the context of the microcracks described above, osteoclastic resorption is first initiated, which is then in turn followed by osteoblastic bone formation. The interaction between osteoblasts, osteoclasts and osteocytes is controlled substantially by the RANKL/OPG signal transduction pathway (differentiation of osteoclasts) and the WNT/DKK/SOST pathway (WNT is a signal protein composed of the wingless (Wg) and Int-1 protein; DKK = dickkopf; SOST = symbol for the protein sclerostin)) (differentiation of the osteoblasts).

There are involved in bone formation especially the WNT pathway for differentiating the osteoblasts and the PTH signal transduction pathway. The differentiation of haematopoetic stem cells to osteoclasts is controlled *via* the RANKL/OPG signal transduction pathway. The osteoclasts are inhibited by zoledronic acid, with the result that no calcium is released from the bone.

Bone serves as the calcium store for the human body and thus plays a crucial part in calcium-phosphate homeostasis. By bone formation and resorption, excess calcium reserves from the blood can be stored or made available again if required.

In various diseases related to bone metabolism, this sensitive equilibrium is disrupted. The most frequent disease related to bone metabolism is osteoporosis. Further diseases which influence bone metabolism are Paget's disease, osteogenesis

imperfecta, primary bone tumours such as multiple myeloma, plasmacytoma, osteosarcoma and bone metastases. Complications due to bone metastases/bone tumours are referred to as "skeletal-related events" (SRE). The term "skeletal-related events" (SRE) includes acute events such as pathological bone fractures, spinal cord compression, bone pain or tumour-induced hypercalcaemia, and also therapeutic interventions such as bone irradiation or surgical interventions in bone, which can be carried out, for example, in patients with bone metastases or primary bone tumours.

Osteoporosis causes a decrease in bone density, which, together with reduced bone quality, leads to an increased risk of bone fracture. The WHO currently defines osteoporosis as a measurable reduction in bone density below -2.5 standard deviations (so-called T-score) from a healthy collective (women, 30 years old), measured by means of DXA (dual-energy X-ray absorptiometry). When a bone fracture has taken place, osteoporosis is said to be manifest. Osteoporosis is thus a systemic disease of bone, which frequently manifests itself by a fracture with inadequate trauma. In Germany, about 6 million people are affected by the common disease of osteoporosis, and osteoporosis patients suffer more than 720,000 fractures every year. Postmenopausal osteoporosis is by far the most frequent cause of vertebral and non-vertebral fragility fractures. The risk of suffering a fracture increases considerably with age.

In only the first 5 years following the menopause, in the absence of oestrogen production, a reduction in bone mass which varies in intensity from individual to individual is observed. The postmenopausal loss of bone mass can amount to up to 15% per year and very quickly results in the first osteoporotic fracture in women with a low peak bone mass.

Inadequate calcium intake and a depleted vitamin D level in the blood lead on balance to a calcium depletion in bone. Moreover, it is to be expected that, with increasing age, further pathomechanisms appear, which directly or indirectly further

bone resorption. By the age of 65, for example, the capacity to absorb calcium ions from food has fallen by about 50% (compared to adolescence). Age-related comorbidities, such as diabetes mellitus, limited kidney function, immobility or glitazone treatment, are only a few examples from the long list of risk factors which have been shown to have an additive effect on bone resorption and thus further the latent progression of osteoporosis.

Figure 1 illustrates that only about a third of the calcium provided in the alimentary canal is reabsorbed. 65-70% of dietary calcium is excreted again with the faeces. The reabsorption process itself can additionally be positively or negatively influenced by various factors. For example, foods that are highly enriched with phosphates can interfere with the uptake of calcium considerably.

The hormones which control calcium homeostasis include, in addition to the sex hormones (oestrogen, testosterone), especially calcitonin, parathormone (parathyrin) and calcitriol (active form of vitamin D3). Calcitriol is essential for allowing the absorption of calcium and phosphate in the small intestine. In addition, calcitriol increases the reabsorption of calcium into the kidneys and stimulates bone mineralization (incorporation of calcium into the bone matrix).

A negative calcium balance occurs, for example, when the body excretes more calcium than it can reabsorb *via* the intestine. If this state persists for a prolonged period of time, increased bone resorption and secondary hyperparathyroidism occur. In order to mobilize the "missing" calcium from bone, "parathormone" is formed in the parathyroid gland. As is shown in Figure 2, parathormone stimulates bone resorption and thus leads to an increase in the calcium concentration in the blood. The calcium concentration thus remains relatively constant in the blood, at the expense of bone, which, in the presence of a calcium deficiency, donates its calcium in order to increase the calcium in the blood.

Figure 3 shows a diagram of "Calcium losses in old age": After the age of only 40, a gradual loss of bone density of 2-3% per year begins in men and women. There can be a considerable increase in the yearly losses in more than 20% of women following the menopause. Often unnoticed, the women affected lose more than a quarter of their bone mass (= calcium) in a relatively short period of time and are thus at a very high risk of fractures over the course of their further lifetime. The disease "osteoporosis" is in many cases diagnosed too late – in most cases only when an osteoporotic fracture (i.e. without a traumatic event) has already occurred, for example in the vertebral body, the hip or the wrist.

An additional problem, which should not be underestimated, for the affected men and women aged 50 and over is the growing calcium gap, which is the result of a progressive negative calcium balance. As is shown in Figure 4, there is an increasing discrepancy in old age between the daily calcium requirement and the actual uptake of calcium from the gastrointestinal tract. The age-related high requirement for calcium is influenced substantially by the following factors: decreasing calcium absorption in the gastrointestinal tract, calcium-poor diet (few dairy products), vitamin D deficiency, less movement, the calcium store "bone" is to be refilled again (formation of new bone mass), increased parathormone in the blood (increased bone resorption and calcium losses) or limited kidney function (reduced calcium reabsorption and less active vitamin D).

For balancing the natural calcium losses *via* the skin and kidneys and for maintaining a constant calcium level in the blood, which is essential for life, the human organism ultimately has only 2 possibilities:

1.) Mobilize calcium from the "calcium store bone". Disadvantage: The resorption of bone substance necessary therefor can lead to losses of stability and fractures in the long term.

2.) Sufficient absorption of calcium from the gastrointestinal tract and reabsorption of calcium into the kidneys. Both are controlled by vitamin D.

The biologically active form of vitamin D (1α,25-dihydroxycholecalciferol; calcitriol) promotes the uptake of calcium from the gastrointestinal tract into the blood. The maximum serum concentration is achieved within three to six hours after uptake. Overall, vitamin D leads to a promotion of the uptake of calcium into the body. An overdosage can lead to vitamin D poisoning, since the body stores vitamin D. Vitamin D poisoning can lead to pronounced demineralization of bone, which leads to fractures. At the same time, high calcium serum concentrations can lead to abnormal calcification of a wide variety of soft tissues. In addition, owing to the increased renal calcium excretion, kidney stones can form.

A vitamin D deficiency, owing to reduced reabsorption from the intestine, leads to less calcium passing into the blood from food.

A calcium and/or vitamin D deficiency is treated by supplementation with preparations containing calcium and vitamin D. However, the administration of calcium and vitamin D is not without controversy. Discussions on the tolerability of calcium are taking place worldwide, and some scientists see calcium supplementation as a cardiovascular risk. It is maintained that calcium increases the risk of cardiovascular events such as myocardial infarction. In Germany, this discussion has led to calcium supplementation frequently being stopped.

For osteoporosis, calcium deficiency means an intensification of the clinical picture with an increase in the risk of fracture.

In manifest osteoporosis, the bone mineral content is reduced (T-score: <-2.5) and fractures have occurred, for example 1 to 3 vertebral body fractures.

Long-term glucocorticoid treatment can lead to severe glucocorticoid- or corticoid-induced osteoporosis with fractures. In the case of an administration of >5 mg prednisone equivalent per day over >3 months, preventive or therapeutic measures are recommended. Especially in the first six months after the start of treatment, in the case of considerable dose increases in the course of the treatment and in the case of long-term treatment with high doses, a significant decrease in bone density is to be expected, which should be taken into consideration in the treatment. Glucocorticoid-induced bone loss has several causes. At the start of treatment, glucocorticoids lead to an increase in bone resorption. Steroids inhibit the proliferation and function of osteoblasts and increase the apoptosis thereof. They thus cause reduced bone neoformation. At the same time, they lead to a negative calcium balance by inhibiting intestinal calcium reabsorption and increasing urinary calcium excretion.

Solid primary tumours, for example mammary, prostate, lung, intestinal or bone carcinoma (e.g. osteosarcoma), can manifest themselves in bone and thus cause bone metastases or bone diseases. Bone metastases are metastases of primary tumours into the bones, where they can lead to pain and fractures. Increased bone resorption or excessive production of inferior bone substance are responsible. This reduces the stability of the bones. Tumour-related bone complications show high morbidity, an increased bone fracture rate, nerve compressions and in some cases excruciating pain. If calcium is increasingly released from the bone and delivered to the blood, tumour-induced hypercalcaemia can develop. Thus, for example, the proportion of patients with moderate or severe bone pain (≥ 4 points in the BPI-SF [brief pain inventory, short form]) with metastasized mammary, prostate, lung, intestinal or bone carcinoma (e.g. osteosarcoma) at over 80%, followed only by neuralgic pain at about 10%, is by far the highest (Cleeland, C.S. *et al.*, Ann. Onc. 2005, 16: 972-980).

The term "multiple myeloma" or "plasmacytoma" or "Kahler's

disease" refers to a cancer of the bone marrow, in which the antibody-producing cells (plasma cells) are greatly multiplied. These malignant plasma cells multiply in an uncontrolled manner and form functionless antibodies or parts thereof. The progression of the disease can very considerably, with moderate to very highly malignant progressions which, without treatment, rapidly lead to the death of the patient. The symptoms are caused by the growth of the cells or by the antibodies, or fragments thereof, that are produced, which can manifest themselves as bone pain, reduction in bone mass and as fractures, accompanied by an increased release of calcium into the blood, which can lead to tumour-induced hypercalcaemia. The number of leucocytes falls, while the large number of antibodies settles in the tissue and leads to functional disorders of many organs, to kidney failure and to impairment of blood flow.

Medicaments for treating diseases related to bone metabolism are known. In the treatment of osteoporosis with medication, the primary aim is to stop the pathological loss of bone mass. The negative balance (imbalance between formation and resorption of bone substance) can be adjusted either by antiresorptive measures, by inhibiting the osteoclasts (bone resorption), or by anabolic measures, by stimulating the osteoblasts (bone formation). Only when formation and resorption processes are in equilibrium with one another again and a sufficient supply of calcium and vitamin D is ensured can new bone mass form and the risk of osteoporotic fractures be reduced.

For the treatment of osteoporosis, on the one hand osteoclastic bone resorption can be inhibited by bisphosphonates such as zoledronic acid; on the other hand, bone formation can be stimulated by anabolic medicaments. The recombinant 1-34 fragment of parathormone is here authorized for the treatment of osteoporosis.

Antiresorptives such as bisphosphonates are at present the standard treatment for metabolic bone diseases which require effective inhibition of bone resorption. This includes the use

of these substance classes for the treatment of osteoporosis and – with significantly higher doses and shorter treatment intervals – for the prevention of tumour-related skeletal complications.

Bisphosphonates such as zoledronic acid bind to bone and are taken up by mature osteoclasts. They inhibit the osteoclasts at the bone surface, that is to say bone resorption is inhibited by the use of bisphosphonates.

Zoledronic acid and derivatives thereof are conventionally used to treat the above-mentioned diseases such as osteoporosis or tumour-related bone diseases.

As a result of the administration of zoledronic acid and inhibition of the osteoclasts, calcium remains in the bone. Stimulation of bone resorption, for example by parathormone, is inhibited to a greater or lesser extent, depending on the zoledronic acid molecules present in the bone. Specifically in the case of the high-dose administration of zoledronic acid (e.g. 4 mg/4 weeks) in oncology, there is a risk of tumour treatment-induced hypocalcaemia. Hypocalcaemia is present when the total calcium in the blood serum is below 2.2 mmol/l (9 mg/dl). As a result of the inhibition of the osteoclasts by medication, the calcium concentration in the blood can be adjusted only by an intake of calcium from outside (orally or intravenously). This is illustrated in Figure 5. PTH activates the release of calcium from bone, which, however, is prevented by the inhibition of the osteoclasts by the zoledronic acid. The intake of calcium from outside is therefore essential.

The risk of hypocalcaemia is increased significantly if secondary hyperparathyroidism is present in the case of vitamin D deficiency. In this frequent vitamin D deficiency state, parathormone is increasingly released in order to adjust the serum calcium level. Parathormone indirectly increases the calcium concentration in the blood plasma by activating the osteoclasts.

The hypocalcaemia is increased by the antiresorptive treatment because the osteoclasts are inhibited.

In particular in the case of the oncological administration of antiresorptives such as zoledronic acid, a shortage of calcium and/or vitamin D can escalate dramatically.

Hypocalcaemia caused in this way can lead to cardiac arrhythmia and, in particularly severe progressions, even to death if the hypocalcaemia is not detected and treated in good time. Moreover, hypocalcaemia remains undetected in many cases, since the calcium level is not measured as a laboratory parameter at short time intervals in outpatient clinical treatment. In order to avert the treatment-related side effect of zoledronic acid, "hypocalcaemia", there is provided herein supplementation with calcium and vitamin D, which can prevent hypocalcaemia during treatment with zoledronic acid.

An unnoticed shortage of calcium and vitamin D can moreover have a negative effect on the overall success of antiresorptive treatment, for example with zoledronic acid, and thus reduce the desired protection against new fractures or even increase the number of fractures if calcium and vitamin D supplementation during antiresorptive treatment is stopped.

WO 2008/116133 A1 discloses dosing regimes containing zoledronic acid and some of its derivatives in combination with calcium and vitamin D, for reducing osteoporotic fractures (page 2, [007]), and a multicomponent kit for a patient with a risk of secondary osteoporotic fractures and a vitamin D deficiency, wherein the kit contains vitamin D or functional analogues thereof, zoledronic acid or a functional analogue and optionally a calcium-containing component (page 2, [008]). WO 2008/116133 A1 does not disclose the treatment or prophylaxis of treatment-related hypocalcaemia but excludes patients with hypocalcaemia from the proposed study (pages 17-18, [0079]).

The patient information for Zometa (FDA prescribing information, published at: https://www.drugs.com/pro/zometa.html, page 5 under the section "Hypocalcemia") discloses *inter alia* hypocalcaemia as a possible side effect of treatment with Zometa, which contains the active ingredient zoledronic acid, as well as the note that calcium should be measured and hypocalcaemia corrected prior to treatment with Zometa. Patients should be adequately supplemented with calcium and vitamin D. The patient information does not indicate how patients are to be adequately supplemented.

The present invention solves these problems and provides novel pharmaceutical compositions of zoledronic acid and calcium and vitamin D and/or derivatives thereof, in order better to treat treatment-related side effects such as hypocalcaemia in diseases of bone metabolism, or to prevent such diseases, and in this manner ensure the optimal action, and also to prevent or guard against improper use.

Summary of the invention

In a first aspect, the invention relates to pharmaceutical compositions comprising zoledronic acid and calcium and vitamin D for use in the treatment and/or prophylaxis of treatment-related hypocalcaemia due to zoledronic acid during treatment of osteoporosis, postmenopausal osteoporosis, manifest osteoporosis, osteoporosis in men or women, characterized in that the pharmaceutical composition comprising zoledronic acid and/or derivative(s) thereof is administered intravenously at a dosage of 4-6 mg, more preferably 5 mg, zoledronic acid once- or twice-yearly and the pharmaceutical composition(s) comprising calcium is/are administered orally at a dosage of 400-600 mg per day, more preferably 500 mg per day, and vitamin D is administered orally at a daily dosage of 800-1200 IU vitamin D, particularly preferably 1000 IU vitamin D.

In a further aspect, the invention relates to pharmaceutical compositions comprising zoledronic acid and calcium and vitamin

D for use in the treatment and/or prophylaxis of treatment-related hypocalcaemia due to zoledronic acid in skeletal-related complications, in particular pathological fractures, irradiation of the bone, spinal cord compression or surgical interventions in bone, bone metastases, pain in bone metastases, nerve entrapment or deformations as a result of one or more solid tumours, for example breast cancer, prostate cancer, lung cancer or multiple myeloma, characterized in that zoledronic acid at a dosage of 3-5 mg, more preferably 4 mg of zoledronic acid intravenously for a 3-4 week period of use and 400-600 mg calcium daily, more preferably 500 mg calcium daily, and 800-1200 IU vitamin D daily, more preferably 1000 IU vitamin D daily, are administered orally.

The invention relates further, in further aspects, to the use of derivatives of zoledronic acid, to the treatment and/or prophylaxis of treatment-related side effects, to various calcium compounds and vitamin D derivatives for use in the above-mentioned implementation examples, and to pharmaceutically suitable excipients and solvents.

Detailed description of the invention

Zoledronic acid is a very effective antiresorptive and is used in the treatment of diseases related to bone metabolism. Despite its effectiveness, treatment with zoledronic acid is encumbered with considerable, in some cases severe side effects. The present invention provides pharmaceutical compositions which considerably improve treatment with zoledronic acid in terms of effectiveness and safety. As well as comprising zoledronic acid, the pharmaceutical compositions comprise calcium and vitamin D.

In the prescribing information for Aclasta (Novartis Pharma, medicament, contains 5 mg zoledronic acid as a solution for infusion which is administered once per year), only a sufficient intake of calcium and vitamin D is recommended; the precise dosage is not given. Aclasta is used in the treatment of osteoporosis *inter alia* in postmenopausal women and adult men

with an increased risk of fractures, including in patients who have recently suffered a low-trauma hip fracture, in the treatment of Paget's disease of the bone in adults, and in the treatment of osteoporosis associated with systemic long-term glucocorticoid treatment in postmenopausal women and in adult men with an increased fracture risk.

Zometa (Novartis Pharma, medicament, contains 4 mg/5 ml or 4 mg/100 ml zoledronic acid as a concentrate for solution for infusion or a solution for infusion) is used in an amount of 4 mg every 3-4 weeks in the prevention of skeletal-related complications (pathological fractures, spinal cord compression, irradiation or operation on the bone, or tumour-induced hypercalcaemia) in adult patients with advanced tumour diseases which have spread to the skeleton, and also in the treatment of adult patients with tumour-induced hypercalcaemia.

The sufficient total daily intake of calcium is 1000 mg. Calcium is taken up *via* food, so that, with a calcium-rich diet, the required daily dose can be achieved. A calcium intake of more than 2500 mg per day is seen as problematic since *inter alia* the risk of formation of kidney stones can increase. As a result of various publications about cardiovascular side effects caused by the excessive intake of calcium, many patients have refrained from taking calcium in a sufficient amount, even during treatment with zoledronic acid.

In many cases, the success of zoledronic acid treatment overall is thus compromised, and the cardiovascular side effects are then caused by the shortage of calcium, or by the pronounced inhibition of the osteoclasts by the zoledronic acid treatment, which inhibits absorption of calcium from bone into the blood.

This leads to hypercalcaemia, which causes cardiovascular side effects. In principle, the exact opposite of the desired success will thus occur. Cardiovascular effects then increasingly occur as a result of the calcium deficiency - not the oversupply of calcium - which could have been prevented by an appropriate

supply of calcium during the treatment with zoledronic acid.

If the diet contains sufficient calcium, supplementation with a pharmaceutical composition comprising 1000-1500 mg of calcium per day will lead to an oversupply of calcium, which increases the risk of cardiovascular side effects. Contrary to the study designs, which in the prescribing information for Aclasta involve a daily dose of 1000-1500 mg calcium, a lower dosage is provided in the present invention in order to treat or prevent hypocalcaemia and cardiovascular side effects.

The preferred amount of calcium in the pharmaceutical composition is 400-600 mg calcium per day, more preferably 500 mg calcium per day, in order on the one hand to maintain a base level of calcium even in the case of a calcium-poor diet, and on the other hand not to fall into an oversupply, which is associated with the mentioned risks and consequently is unacceptable for the patients. According to the result report of the "Nationale-Verzehrs-Studie II" [national dietary study II] conducted in Germany, 46% of men and 55% of women do not achieve the recommended daily intake of calcium. In the age group between 51-80 years, the average total intake is in the range between 490-1790 mg calcium per day.

According to the prescribing information for Zometa, 500 mg of calcium should be taken per day, but in combination with 400 IU vitamin D per day. The studies for Zometa were directed at US patients. In the USA, a large number of foods are supplemented with vitamin D, for example milk, orange juice, breads or breakfast cereals. In Germany and the EU, this is substantially not the case, so that, according to the invention, a higher amount of vitamin D of 800-1200 IU per day is provided, more preferably 1000 IU vitamin D per day. The higher amount of vitamin D is capable of promoting the transport of a potentially smaller amount of calcium from the gastrointestinal tract into the blood and of achieving an adequate calcium serum level despite the smaller amount of calcium.

The vitamin D level is readily able to be measured. The combination according to the invention is provided for a vitamin D serum concentration which is not below 20 ng/ml (50 nmol/l serum).

In the case of a severe deficiency (< 10 ng/ml serum), 200,000 IU over 10 days and then 20,000 IU weekly should be substituted. In the case of a significant deficiency (10-20 ng/ml serum), an initial substitution of 100,000 IU should be made, followed by a maintenance of 20,000 IU/week. If a deficiency (21-30 ng/ml serum) is present, a substitution of 20,000 IU/week should be made. If the normal vitamin D levels (31-60 ng/ml serum) are achieved, the daily substitution according to the invention of 800-1200 IU vitamin D, more preferably 1000 IU, can be used.

Supplementation with 400 IU vitamin D is not sufficient to maintain the vitamin D level in the normal range of 31-60 ng/ml serum on administration of the pharmaceutical composition according to the invention of zoledronic acid and calcium.

In this manner, hypocalcaemia is prevented by the pharmaceutical composition according to the invention comprising zoledronic acid, calcium and vitamin D.

The term "zoledronic acid" or "zoledronate" ($C_5H_{10}N_2O_7P_2$; [1-hydroxy-2-(imidazol-1-yl)ethylidene]diphosphonic acid, CAS number: 118072-93-8) additionally includes all known pharmaceutically compatible derivatives of zoledronic acid. It is known to the person skilled in the art that salts can be present as solvates, for example hydrates, or that zoledronic acid can be present in the form of esters. Zoledronic acid can be provided in any pharmaceutically compatible salt or acid form. Salts are preferred, since membranes are attacked less by salts. Preferred salts are in particular, without implying any limitation, zoledronic acid disodium salt tetrahydrate ($C_5H_8N_2Na_2O_7P_2 \bullet 4H_2O$), CAS number: 165800-07-7), zoledronic acid trisodium salt hydrate $(C_5H_7N_2Na_3O_7P_2 \bullet H_2O)_5$, CAS number: 165800-08-8, salts with monovalent cations, in particular zoledronate

sodium and/or esters, in particular ethyl, propyl, isopropyl, n-butyl and t-butyl esters.

According to the invention, the pharmaceutical composition comprising zoledronic acid is administered in the field of osteoporosis, postmenopausal osteoporosis, osteoporosis in men or women intravenously at a dosage of 4-6 mg, preferably 5 mg, once-/twice-yearly.

According to the invention, the pharmaceutical composition comprising zoledronic acid is administered in the field of oncology at a dosage of 3-5 mg, preferably 4 mg, intravenously for a 3-4 week period of use.

The term "calcium" includes all known pharmaceutically acceptable calcium compounds, in particular, without implying any limitation, calcium citrate, further names: tricalcium citrate, TCC, tricalcium dicitrate, tricalcium di-[2-hydroxy-1,2,3-propanetricarboxylate]-tetrahydrate, E 333, $C_{12}H_{10}Ca_3O_{14}$, CAS numbers: 813-94-5 (anhydrous), 5785-44-4 (tetrahydrate); calcium gluconate monohydrate ($C_{12}H_{22}CaO_{14} \bullet H_2O$, CAS numbers: 299-28-5 (anhydrous) and 66905-23-5 (monohydrate)); calcium lactate gluconate, a double salt of lactic and gluconic acid, which is in the form of a mixture, further names: CLG, calcium lactate gluconate, calcium lactogluconate, E 327, E 578, CAS numbers: 11116-97-5, 814-80-2 (calcium lactate pentahydrate), 18016-24-5 (calcium gluconate monohydrate), or calcium carbonate $CaCO_3$, CAS number: 471-34-1, calcium phosphate, calcium dihydrogen phosphate, calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate, calcium acetate, calcium ascorbate, calcium chloride, calcium glucoheptonate, calcium glycerophosphate and/or calcium sulfate.

The term "vitamin D" includes vitamin D or derivatives thereof, in particular, without implying any limitation, vitamin D3 (cholecalciferol, $C_{27}H_{44}O$, CAS number: 67-97-0), calcitriol (1,25-dihydroxyvitamin D3, 1α,25-dihydroxycholecalciferol, 1,25$(OH)_2$vitamin D3, 1,25$(OH)_2$D3, (5Z,7E)-(1S,3R)-9,10-

secocholesta-5,7,10(19)-triene-1,3,25-triol, CAS number: 32222-06-3) or 1α,25-dihydroxycholecalciferol (biologically active form of vitamin D3), alphacalcidol (1α-hydroxyvitamin D3), 24,25-dihydroxyvitamin D3 or calcifediol (25-hydroxyvitamin D3 25-hydroxycholecalciferol, CAS number: 19356-17-3, IUPAC name: (6R)-6-[(1R,3aR,4E,7aR)-4-[(2Z)-2-[(5S)-5-hydroxy-2-methylidenecyclohexylidene]ethylidene]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-1-yl]-2-methylheptan-2-ol), vitamin D2 (3β-5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol, calciferol, ergo-calciferol, CAS number: 50-14-6 or the biologically active forms thereof.

Both vitamin D preparations, and zoledronic acid and calcium are commercially available, and the methods for their preparation are known to the person skilled in the art.

There are provided pharmaceutical compositions comprising zoledronic acid, calcium and vitamin D for use in the treatment and/or prophylaxis of treatment-related hypocalcaemia due to zoledronic acid during treatment of osteoporosis, postmenopausal osteoporosis, manifest osteoporosis, osteoporosis in men or women, which are administered orally at a zoledronic acid concentration of 4-6 mg once- or twice-yearly, more preferably 5 mg once- or twice-yearly, and 400-600 mg calcium daily, more preferably 500 mg calcium daily, and 800-1200 IU vitamin D, more preferably 1000 IU vitamin D, daily.

In a further exemplary embodiment there are provided pharmaceutical compositions comprising 3-5 mg, more preferably 4 mg, zoledronic acid intravenously for a 3-4 week period of use and 400-600 mg calcium daily, more preferably 500 mg calcium daily, and 800-1200 IU vitamin D, more preferably 1000 IU vitamin D, for use in the treatment and/or prophylaxis of treatment-related hypocalcaemia due to zoledronic acid in skeletal-related complications, in particular pathological fractures, spinal cord compression, irradiation or operation on bone, pain in bone metastases as a result of one or more solid tumours, for example mammary carcinoma, prostate carcinoma, lung cancer, multiple

myeloma.

In one exemplary embodiment, the amounts of zoledronic acid indicated above are provided in a solution for infusion of 5 ml to 100 ml, more preferably as a 5 ml concentrate for solution for infusion or as a 100 ml ready-to-use solution for infusion in a pharmaceutically suitable solution, for example isotonic saline, isotonic mannitol-sodium citrate solution or other pharmaceutically suitable isotonic solutions.

In a further exemplary embodiment, calcium and vitamin D are provided with pharmaceutically suitable excipients, in particular lactose, starch, acidification agents, in particular citric acid and malic acid, acidity regulators, in particular sodium hydrogen carbonate and sodium carbonate, humectants, in particular sorbitol, xylitol and inulin, release agents, in particular tricalcium phosphate, fatty acids, in particular magnesium salts, in particular magnesium stearate, natural and nature-identical and other flavours and flavourings, sweeteners, in particular sodium cyclamate, aspartame and saccharin sodium, maltodextrin, colorants, in particular beetroot juice powder and riboflavin-5' phosphate, silica, in particular colloidal hydrated silica, phenylalanine, gum arabic, sucrose, gelatin, maize starch, soybean oil, glycerol, DL-alpha-tocopherol, isomalt, sodium hydrogen carbonate, sodium dihydrogen carbonate, sodium citrate, sodium dihydrogen citrate, carmellose sodium, acesulfame potassium, sodium ascorbate, triglycerides, in particular medium-chain, and/or in pharmaceutically compatible fluids, in particular water, isotonic saline or isotonic glucose solution or other pharmaceutically suitable solutions.

In a further exemplary embodiment, zoledronic acid, calcium and/or vitamin D are provided individually or together, optionally with pharmaceutically suitable excipients and/or fluids, in particular as effervescent tablets, tablets or capsules to be swallowed, chewable tablets, effervescent granules, direct granules, solutions for drinking, drops, sublingual sprays, as concentrates for solutions for infusion,

ready-to-use solutions for infusion, concentrates for solutions for injection, solutions for injection or prefilled syringes.

The following figures and examples serve to illustrate the invention, but without limiting the invention to the figures or examples.

Figures:

Figure 1: shows a diagram of the calcium intake from the gastrointestinal tract into the blood and into the bone, and also the influencing factors which promote or reduce calcium uptake.

Figure 2: shows the consequences of an insufficient calcium uptake from food.

Figure 3: shows the increase and decrease in bone mass over the course of a human lifetime, and the increased risk of bone fracture in old age as bone mass decreases.

Figure 4: shows the increased calcium requirement with increasing age as a result of reduced actual calcium uptake.

Figure 5: Hypocalcaemia is present if the total calcium in the blood serum is below 2.2 mmol/l (9 mg/dl). Owing to the inhibition of osteoclasts by medication, the calcium concentration in the blood can be adjusted only *via* an intake of calcium from outside (orally or intravenously). This is illustrated in Figure 5.

Example 1:

A vitamin D deficiency is a frequent diagnosis in osteological practice. At the start of the treatment, 89 of 423 patients had a vitamin D deficiency, which was below the value of 20 ng/ml serum, or 50 nmol/l. The maintenance dose was 1000 IU vitamin D daily. A maintenance dose of 400 IU vitamin D daily was not

sufficient to maintain the vitamin D level at the normal value.

Table 1 shows that a maintenance dose of 1000 IU vitamin D is suitable for maintaining the vitamin D level in the normal range:

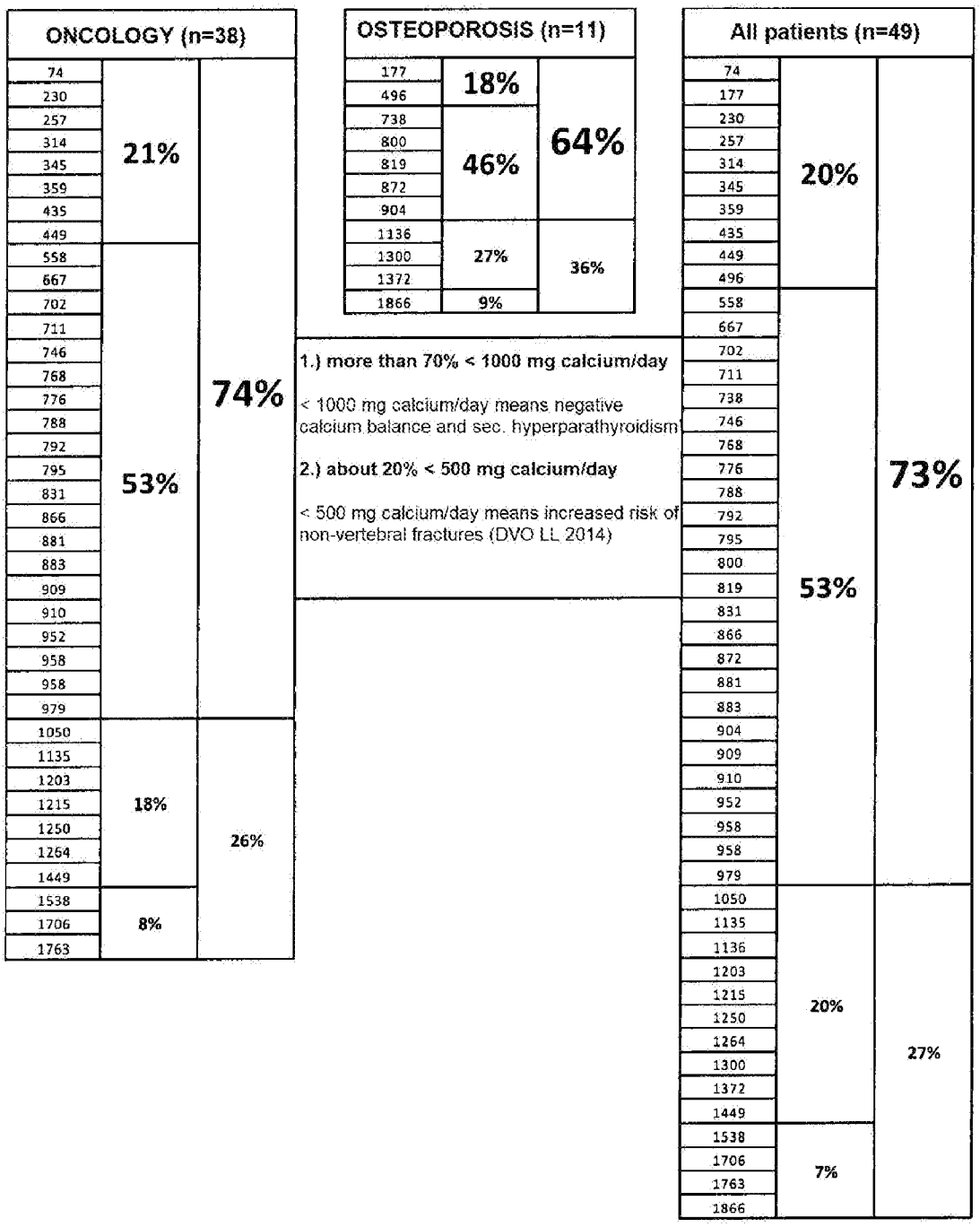
Table 1:

Patient	Vitamin D starting value	Vitamin D value at maintenance dose of 1000 IU vitamin D daily
85 years old, female	9.4 ng/ml	25.5 ng/ml
65 years old, female	8.8 ng/ml	23.4 ng/ml
77 years old, female	12.4 ng/ml	29.2 ng/ml
81 years old, female	10.4 ng/ml	30.4 ng/ml
75 years old, female	14.6 ng/ml	28.8 ng/ml
86 years old, female	10.9 ng/ml	23.7 ng/ml
81 years old, female	8.6 ng/ml	23.2 ng/ml
71 years old, female	17.1 ng/ml	30.5 ng/ml

Example 2:

The vitamin D level of a further 37 patients was analysed. At the start of the treatment, a vitamin D deficiency [25(OH)VitD serum level < 30 ng/ml serum, or 75 nmol/l] was present in about 51% of patients (n = 19). In 27% of patients (n = 10), the 25(OH)VitD serum level was below 20 ng/ml serum, or 50 nmol/l (= severe vitamin D deficiency). The following table 2 shows in the left-hand column in each case the daily uptake of calcium from food in mg. A daily intake of less than 1000 mg from food leads to a negative calcium balance. Secondary hyperparathyroidism develops therefrom, and bone substance is lost. A daily supply of less than 500 mg of calcium is associated with an increased fracture risk for non-vertebral fractures.

Table 2:



Example 3:

The following patient case history shows that the pharmaceutical composition according to the invention of 5 mg zoledronic acid administered intravenously once-yearly, 500 mg calcium daily and 1000 IU vitamin D daily taken orally effectively prevents treatment-related hypocalcaemia caused by treatment with zoledronic acid. The values originate from a 73-year-old female

patient with manifest osteoporosis and a previous low-trauma vertebral body fracture. Both the calcium values and the values for vitamin D are in the normal range during treatment with the pharmaceutical compositions according to the invention.

Following Table 3: Patient case history

Date	Ca in mmol/l	25(OH) vitamin D3 serum level in ng/ml
21.08.12	2.21	30.40
12.03.13	2.36	28.40
08.08.13	2.27	47.30
18.02.14	2.27	34.30
24.07.14	2.23	34.30
19.03.15	2.25	39.10
23.02.16	2.32	29.00

Example 4:

The following data from 10 oncology patients (prostate carcinoma or mammary carcinoma) in Table 5 show the serum levels of calcium and vitamin D3 on administration of 4 mg zoledronic acid monthly, and oral intake of 500 mg calcium daily and 1000 IU vitamin D3 daily.

Table 4: The patients received 4 mg zoledronic acid/month, 500 mg calcium supplementation daily and 1000 IU vitamin D3 daily:

Patient	Calcium mmol/l	25(OH) vitamin D3 serum level; µg/l	after weeks	Calcium	25(OH) vitamin D3 serum level; µg/l	Calcium in diet mg/day
1	2.09	17.2	16	2.14	37.1	1449
2	2.4	17.2	4	2.31	24.3	979

3	2.02	12.1	16	2.22	25.2	958
4	2.37	no data	8/16/20	2.46/2.46/2.32	33.1 after 20 weeks	702
5	2.36	no data	4/16/24	2.41/2.4/2.54	22.3 after 20 weeks	230
6	2.4	no data	4/8/16	2.26/2.41/2.4	no data/ 19.8/22.8	952
7	2.47	no data	4/9/13	2.26/2.4/2.36	40.3 after 13 weeks	1215
8	2.42	22	8/12/16	2.34/2.41/2.4	no data	909
9	2.48	46.7	4/8/12/ 16	2.3/2.34/2.38/ 2.41	46.2/no data/no data/48.1	544
10	2.25	no data	4/8/12/ 16	2.31/2.29/2.34/ 2.28	no data	1250

Table 5: The following patients in Table 5 were suffering from osteoporosis and received 5 mg zoledronic acid/year, 500 mg calcium supplementation daily and 1000 IU vitamin D3 daily:

Patient	Calcium mmol/l	25(OH) vitamin D3 serum level; µg/l	after weeks	Calcium	25(OH) vitamin D3 serum level; µg/l	Calcium in diet mg/day
11	2.28	23.1	24	2.24	40.1	872

12	2.41	15	24	2.4	25.8	1866
13	2.4	21.5	24	2.37	28.6	738
14	2.32	31.3	24	2.44	45.4	800

In the case of a 25(OH) vitamin D serum level < 20 ng/ml, a severe vitamin D deficiency is present, which, according to the DVO guideline, means an increased risk of fracture. The data in Example 5 show that the combination according to the invention is suitable for normalizing the vitamin D level above 20 ng/ml, or 20 µg/l, and thus lowering the risk of fracture.

The calcium serum level is generally in the normal range in patients with osteoporosis. In oncology patients, the calcium concentration in the blood can increase (= tumour-induced hypercalcaemia) or decrease as a result of treatment (treatment-induced hypocalcaemia). Patients with a calcium-poor diet therefore have an additional risk of hypocalcaemia. A daily supplementation according to the invention with 500 mg calcium ensures a well-adjusted calcium balance.

An increased PTH level (= secondary hyperparathyroidism) and hypocalcaemia – induced by antiresorptive treatment with zoledronic acid – are risk factors for the development of necrosis at the jaw bone.

Patients treated with the combination according to the invention were free of side effects; in particular, there was no osteonecrosis of the jaw, non-healing wounds leading to dissolution of the jaw, hypocalcaemia, cardiovascular side effects such as myocardial infarction, atrial fibrillation, arrhythmias, cramps and/or numbness.

Furthermore, no skeletal-related complications occurred, in particular no pathological fractures, irradiation of the bone, spinal cord compression or surgical interventions at the bone, bone metastases, pain in bone metastases, nerve entrapment or deformations as a result of one or more solid tumours, for example breast cancer, prostate cancer, lung cancer or multiple

myeloma, and also no fractures.

Patentkrav

1. Farmaceutiske præparater omfattende zoledronsyre og kalcium og D-vitamin til anvendelse ved behandling og/eller profylakse af den af zoledronsyre terapibetingede hypokalcæmi ved behandlingen af osteoporose, postmenopausal osteoporose, manifest osteoporose, osteoporose hos mænd eller kvinder, kendetegnet ved, at det farmaceutiske præparat omfattende zoledronsyre administreres intravenøst i en dosering på 4-6mg, mere foretrukket 5mg zoledronsyre årligt eller halvårligt, og det/de farmaceutiske præparat(er) omfattende kalcium administreres oralt med en dosering på 400-600mg pr. dag, særligt foretrukket 500mg pr. dag, og D-vitamin administreres oralt i en dosering på 800-1.200 I.E. D-vitamin, særligt foretrukket 1.000 I.E. D-vitamin dagligt.

2. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ved behandling og/eller profylakse af den af zoledronsyre terapibetingede hypokalcæmi ved skeletrelaterede komplikationer, navnlig patologiske frakturer, bestråling af knoglerne, rygmarvskompression eller operative indgreb i knoglerne, knoglemetastaser, smerter ved knoglemetastaser, indeklemte nerver eller deformeringen på grund af en eller flere solide tumorer såsom eksempelvis brystkræft, prostatakræft, lungekræft eller multipelt myelom, kendetegnet ved, at zoledronsyre administreres intravenøst i en dosering på 3-5mg, mere foretrukket 4mg zoledronsyre til 3-4 ugentlige anvendelser og 400-600mg kalcium oralt dagligt, særligt foretrukket 500mg kalcium dagligt, og 800-1.200 IE D-vitamin dagligt, særligt foretrukket 1.000 IE D-vitamin dagligt.

3. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge krav 1-2, idet zoledronsyre omfatter farmaceutisk egnede salte og/eller estere, navnlig salte med monovalente kationer, navnlig zoledronat-natrium og/eller ester, navnlig ethyl-, propyl-, isopropyl, n-butyl- og t-butyl-ester.

4. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge krav 1-3, idet kalcium navnlig omfatter kalciumlaktatgluconat, kalciumgluconat-monohydrat, kalciumlaktat-pentahydrat, kalciumzitrat, kalciumzitrat-tetrahydrat, kalciumkarbonat, kalcium-phosphat, kalcium-dihydrogenphosphat, kalcium-hydrogenphosphat, kalcium-hydrogenphosphat dihydrat, kalcium-acetat, kalcium-ascorbat, kalcium-chlorider, kalcium-glucoheptonat, kalcium-glycerophosphat og/eller kalcium-sulfat.

5. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge krav 1-4, idet D-vitamin navnlig omfatter D-vitamin og/eller D3-vitamin og/eller D2-vitamin og/eller derivater heraf, navnlig calcitriol (1,25-dihydroxyvitamin D3) eller 1α, 25-dihydroxycholecalciferol, alphacalcidol (1α-hydroxyvitamin D3), 24,25-dihydroxyvitamin D3, calcifediol, D2-vitamin og/eller ergocalciferol.

6. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge kravene 1-5 endvidere omfattende farmaceutisk egnede hjælpestoffer og/eller væsker eller opløsningsmidler.

7. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge kravene 1-6, idet hjælpestofferne til de farmaceutiske præparater omfatter laktose, stivelse, forsuringsmidler, navnlig citronsyre, æblesyre, syreregulatorer, navnlig natriumhydrogencarbonat og natriumcarbonat, fugtholdningsmidler, navnlig sorbitol, xylitol og inulin, skillemidler, navnlig tricalciumphosphat, spisefedtsyrer, navnlig magnesiumsalte, navnlig magnesiumstearat, naturlige og naturidentiske og andre aromaer og aromastoffer, sødestoffer, navnlig natrium-cyclamat, aspartam og saccharin-natrium, maltodextrin, farvestoffer, navnlig rødbedesaftpulver og riboflavin-5'-phosphat, siliciumdioxid, navnlig højdisperst siliciumdioxid hydrat, phenylalanin, gummi arabica, saccharose, gelatine, majsstivelse, sojaolie, glycerol, DL-alpha-tocopherol, isomalt,

natriumhydrogencarbonat, natriumdihydrogencarbonat, natriumcitrat, natriumdihydrogencitrat, Carmellos natrium, acesulfam kalium, natriumascorbat, triglycerider, navnlig mellemkædede og/eller i farmaceutisk forligelige væsker, navnlig vand, isotonisk kogesalt- eller glucoseopløsning.

8. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge kravene 1-7, idet de farmaceutisk egnede opløsningsmidler eller væsker omfatter vand, isotonisk kogesaltopløsning, isotonisk mannitol-natriumacetatopløsning eller glucoseopløsning.

9. Farmaceutiske præparater indeholdende zoledronsyre og kalcium og D-vitamin til anvendelse ifølge kravene 1-8, idet det farmaceutiske præparat omfattende zoledronsyre tilvejebringes som infusion, infusionsopløsningskoncentrat, færdiginfusion eller færdigfyldt sprøjte, og de farmaceutiske præparater omfattende kalcium og/eller D-vitamin tilvejebringes i fast eller flydende form som brusetablet, synketablet eller -kapsel, tyggetablet, brusegranulat, direkte granulat, drikkeopløsning, dråber, sublingualspray, enkeltvis eller sammen.

Figure 1:

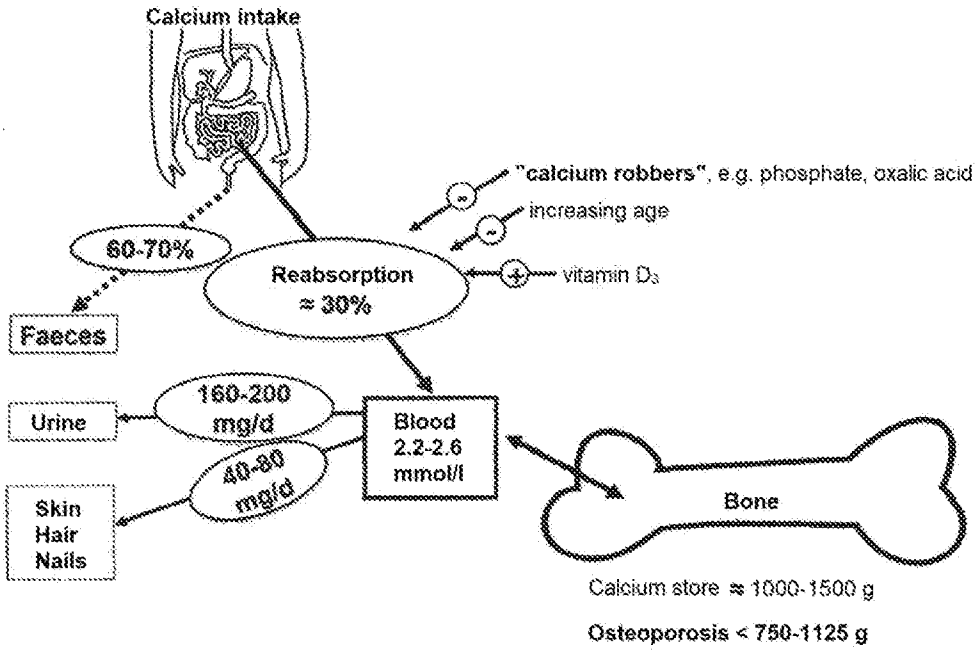


Figure 2:

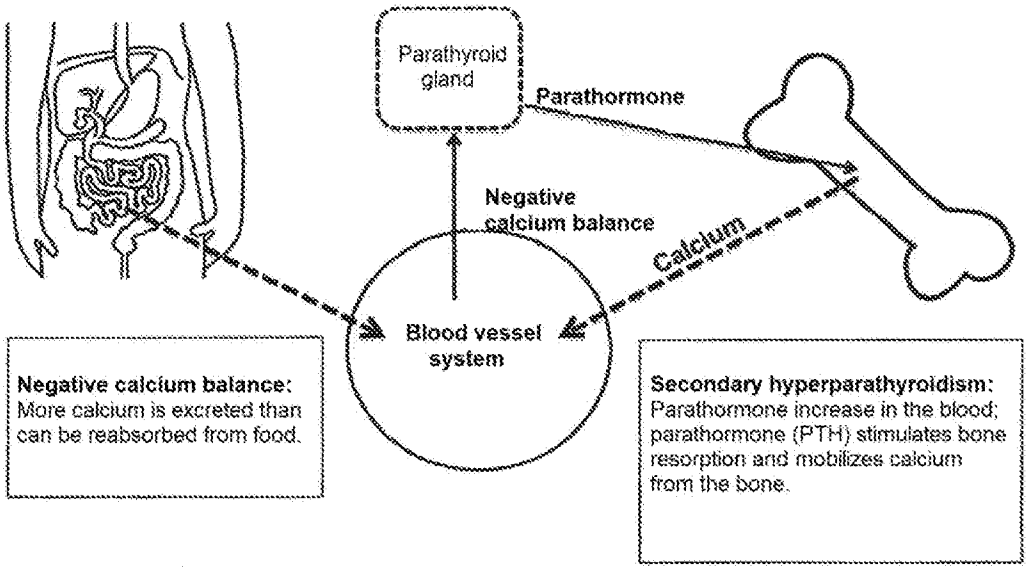


Figure 3:

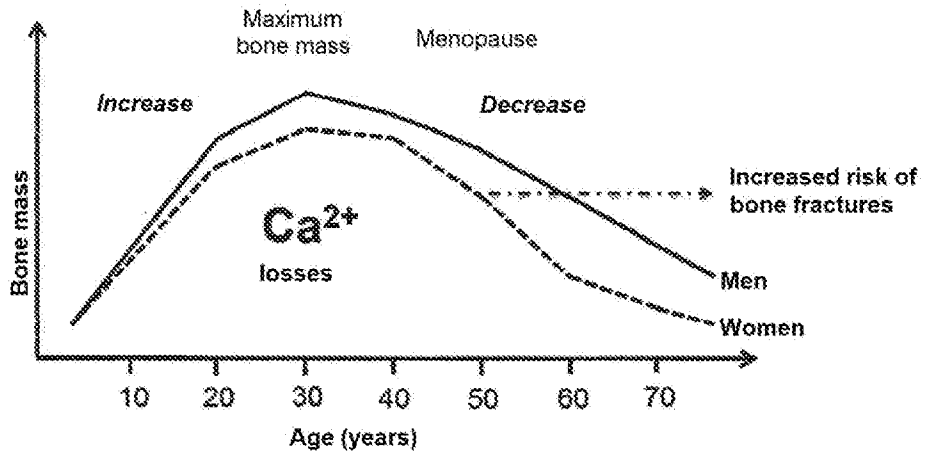


Figure 4:

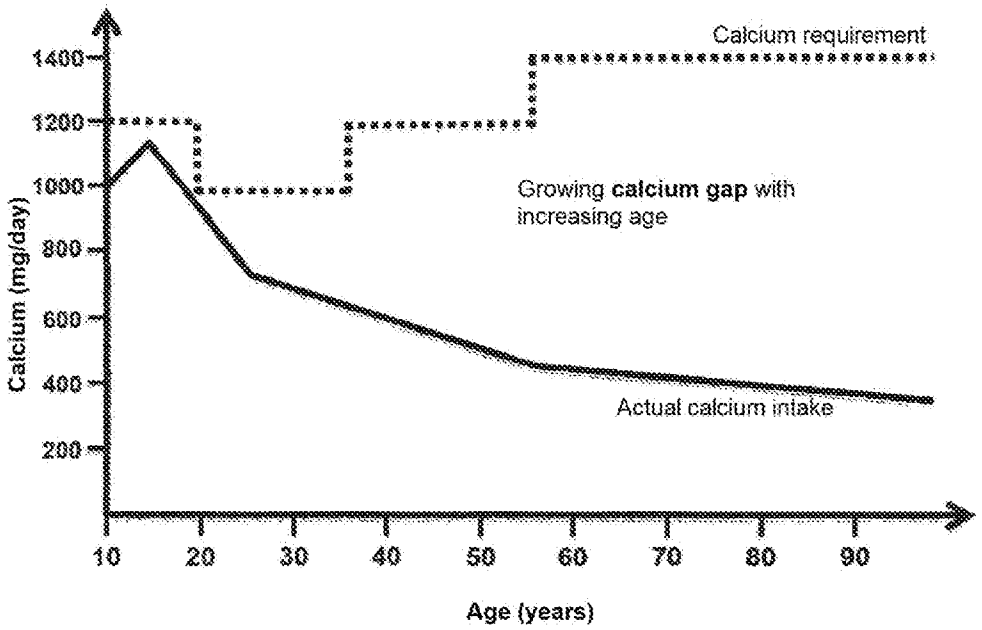


Figure 5: