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Clinical efficacy and safety of use of alfacalcidol and calcitriol in daily endocrinological practice

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Abstract

This paper aims to discuss and compare 2 vitamin D derivatives available on the Polish market, alfacalcidol and calcitriol, in the context of their effectiveness and safety in endocrine patients. Both above-mentioned substances find a number of applications, including in hypoparathyroidism, which is one of the most common indications for their use. We would also like to draw the reader's attention to the fact that there are quite a lot of reports in the literature on the positive effect of alfacalcidol and calcitriol on maintaining bone mass and the risk of fractures, which may bring additional potential benefits to our patients. **(Endokrynol Pol 2023; 74 (1): 16–24)**

Key words: *alfacalcidol; calcitriol; endocrinology; hypoparathyroidism; hypocalcaemia*

Introduction

This paper aims to discuss and compare 2 vitamin D derivatives available on the Polish market, alfacalcidol and calcitriol, in the context of their effectiveness and safety in endocrine patients. Both above-mentioned substances find a number of applications, including in hypoparathyroidism, which is one of the most common indications for their use. We would also like to draw the reader's attention to the fact that there are quite a lot of reports in the literature on the positive effect of alfacalcidol and calcitriol on maintaining bone mass and the risk of fractures, which bring additional potential benefits to our patients.

Calcitriol

Calcitriol (1α,25-dihydroxycholecalciferol — 1α,25$(OH)_2$D) is an active metabolite of vitamin D, formed mainly in the kidneys by hydroxylation of the calcidiol molecule (25-hydroxycholecalciferol — 25[OH]D) in the α position. This reaction is catalysed by 1α-hydroxylase (CYP27B1) [1]. The activity of 1α-hydroxylase depends on several factors, including calcium, parathormone (PTH), fibroblast growth factor 23 (FGF-23), and Klotho concentrations and, on the principle of a negative feedback loop, on 1α,25$(OH)_2$D [2, 3].

Calcitriol triggers processes that increase serum calcium concentrations by enhancing the synthesis of calcium transport protein (CaBP, *calcium binding protein*) from the lumen of the gastrointestinal tract into the blood. The actions of calcitriol in bones include the stimulation calcium and phosphate release (in hypocalcaemia), while in the renal tubules, calcitriol, together with PTH, promotes the reabsorption of calcium. The main pro-calcaemic effect of calcitriol is the inhibition of PTH secretion by the parathyroid glands, both indirectly (an increase in calcium ion concentration) and directly (an inhibition of PTH secretion by calcitriol through a feedback loop mechanism), resulting in increased serum calcium and phosphate concentrations [4].

The effect of calcitriol on bone metabolism is also known, being mediated by the receptor-activator of nuclear factor kappa beta (RANK)/RANK ligand (RANKL) system responsible for osteoclastogenesis. Indeed, calcitriol has been shown to increase RANKL expression in osteoblasts, which, in turn, activates RANK receptors on osteoclast precursors. A consequence of this is the formation of a mature osteoclast with the ability to dissolve and resorb bone tissue, resulting in the release of calcium and phosphate from the bones [5].

Calcitriol acts on the body's cells and tissues, mainly via the vitamin D receptor (VDR) located in the cell nucleus. The active form of vitamin D binds to VDR in the cell nucleus, forming a heterodimer with the 9-cis retinoic acid receptors (RXR, retinoid X receptors), which acts as a transcription factor, thereby initiating genomic actions [6]. It is estimated that calcitriol is thus involved in the regulation of several hundred genes involved in multiple metabolic pathways in the human

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body [7, 8]. The non-genomic actions are mediated by calcitriol binding to VDR, located in the hollows of cell membranes, which is distinct from the nuclear receptor and activates intracellular signal transduction pathways, among others, via kinases, phosphatases, and ion channels [9, 10].

Due to the presence of the VDR receptor on many cells and tissues, also unrelated to bone metabolism, calcitriol has been shown to have immunomodulatory, anticancer, neuroprotective, anti-inflammatory, insulin-stimulating, or blood pressure-controlling effects, in addition to its effect on the calcium-phosphate metabolism [11].

Calcitriol is commonly used for the treatment of severe or progressive recurrent secondary hyperparathyroidism, a disease leading to renal osteodystrophy with moderate to severe chronic renal failure, and hypocalcaemia, caused by hypoparathyroidism (postoperative, idiopathic, and pseudohypoparathyroidism) and hereditary hypophosphataemic rickets (HPDR) [12]. In the year 2009, the Food and Drug Administration (FDA) approved a calcitriol ointment for the topical treatment of mild to moderate plaque psoriasis in adults [13]. The off-label indication for calcitriol includes a treatment and prevention of primary or glucocorticosteroid (GCS)-induced osteoporosis (GIOP) [14].

Calcitriol is hydroxylated and oxidised in the kidney and liver by CYP24A1, a specific cytochrome P450 isoenzyme [15]. The elimination half-life of calcitriol from serum is 3 to 6 hours. However, the pharmacological effect of a single dose of calcitriol persists for 3 to 5 days. Calcitriol is excreted through the gallbladder and is subject to an ileo-hepatic cycle.

Alfacalcidol

Alfacalcidol (1-α-hydroxycholecalciferol) is a synthetic precursor of calcitriol, an active vitamin D3 metabolite, introduced into clinical practice in the early 1970s [16]. Hydroxylation with carbon C25 in the liver produces a biologically active 1α,25(OH)2D [17]. Alfacalcidol contains a hydroxyl group in the α position at the C1 carbon atom. Therefore, it does not hydroxylate in this position in the kidney. This is particularly important in persons with impaired renal function, where hydroxylation in renal tissue is either impossible or impaired.

Alfacalcidol is rapidly metabolised in the liver to calcitriol, so one may say that the 2 substances should demonstrate a very similar clinical effect. Following alfacalcidol administration, bone matrix synthesis and bone growth factors are increased, osteomalacia is reduced, and the incidence of trabecular fractures is reduced [18].

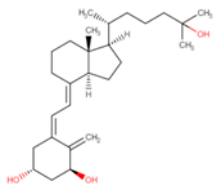
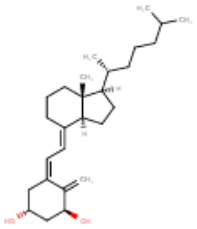
Alfacalcidol administration is indicated in the prevention and treatment of rickets and osteomalacia resistant to vitamin D3, in the course of vitamin D-resistant postmenopausal or senile osteoporosis, hypocalcaemia (especially in patients with diseases leading to impaired 1α-hydroxylation of vitamin D in the kidneys), calcium metabolism disorders in patients with chronic renal failure, renal origin osteodystrophy, hypoparathyroidism, and nephrotic syndrome in children after long-term GCS therapy [19, 20].

Alfacalcidol, like other compounds of the vitamin D group, is well absorbed from the gastrointestinal tract, especially in the presence of bile acid salts. Approximately 50% of the administered dose of alfacalcidol is hydroxylated to calcitriol, i.e. the active form. Calcitriol, produced from alfacalcidol, appears in plasma as early as 25 min after the drug administration and is transported in a form bound to the vitamin D binding protein (DPB). The half-life of alfacalcidol is, according to Mazzaferro et al., about 12 h (i.e. the time necessary for its entire conversion) [21], while other sources estimate it at 3–5 hours [18]. However, this does not reflect the decrease in the content of the compound in the body because most of the metabolite is found intracellularly in a receptor-bound form. Following an oral intake of calcitriol, the maximum serum concentrations are reached within 2 hours, whereas the oral intake of alfacalcidol results in a slow increase in serum calcitriol concentrations, with their peak values to be expected after 8–18 hours [17]. Once absorbed, calcitriol acts directly on the VDR receptor in intestinal mucosal cells to promote calcium absorption, leading to a rapid increase in serum calcium concentrations. In contrast, alfacalcidol activation requires earlier 25-hydroxylation in the liver, which prolongs its action in the gastrointestinal tract [22]. The half-life of calcitriol elimination from the body, corresponding to the half-life of its biological activity, is estimated to be approximately 36 h. Both alfacalcidol and calcitriol are metabolised mainly in the liver; they are excreted as inactive metabolites with the bile and faeces, but only in small amounts with the urine.

Indications for the application of calcitriol and alfacalcidol

The 2 compounds discussed — both being vitamin D analogues – differ significantly in their indications for use, based on their label specifications/registration (Tab. 1), with calcitriol designated only for adults. One of the main indications for the inclusion of the 2 aforementioned vitamin D analogues in therapy is hypoparathyroidism resulting from various causes. Calcium agents and vitamin D analogues should be used in all

Table 1. *Comparison of calcitriol and alfacalcidol characteristics*

	Calcitriol	Alfacalcidol
		
Indications	Severe or progressive secondary hyperparathyroidism leading to renal osteodystrophy with moderate to severe chronic kidney failure Hypocalcaemia due to hypoparathyroidism (postoperative, idiopathic and pseudohypoparathyroidism) Hereditary hypophosphataemic rickets	Postmenopausal and senile osteoporosis with concomitant deficiency of vitamin D or its active metabolites Hypocalcaemia, especially in patients with conditions leading to impaired vitamin D hydroxylation in the kidneys Vitamin D-resistant rickets and osteomalacia Hypoparathyroidism Renal osteodystrophy Calcium metabolism disorders in patients with chronic kidney failure Nephrotic syndromes in children after long-term glucocorticosteroid treatment
Dosage	Secondary hyperparathyroidism, hypoparathyroidism, hereditary hypophosphataemic rickets (HHR): an initial dose of 0.25 μg per day. In the absence of a satisfactory response, the daily dose can be increased by 0.25 μg at 2–4-week intervals In patients with either normal or only slightly reduced calcium levels, doses of 0.25 μg every other day are sufficient The majority of patients respond to a dose of 0.5 μg to 1.0 μg per day The maximum cumulative total dose should not exceed 12 μg per week	The dose should be adjusted individually, depending on the patient's condition Osteoporosis: adults > 40 kg b.w. 0.5–1 μg 1 ×/d with adequate calcium supplementation Nephrotic syndrome in children after long-term glucocorticosteroid therapy: children < 20 kg b.w. 0.25 μg 1 ×/d, 20–40 kg b.w. — 0.25–0.5 μg 1 ×/d Other indications: adults and children > 40 kg b.w. usually 0.5–1 μg 1 ×/d, children 20–40 kg b.w. — 0.25–0.5 μg/d, < 20 kg b.w. — 0.25 μg/d
Pharmacodynamics	An active metabolite of vitamin D, produced mainly in the kidneys by hydroxylation of the calcidiol molecule Binding to VDR receptors, found in the kidneys, parathyroid glands, intestines, and bones, calcitriol increases serum calcium concentrations by promoting its absorption in the intestines, reabsorption in the renal tubules in the kidneys, and release from the bones	A synthetic precursor of the active metabolite of vit. D3 (calcitriol), containing a hydroxyl group in the a position at C1 Its pharmacological activity depends on rapid biotransformation (25-hydroxylation) in the liver to calcitriol, which then binds to VDR receptors in various tissues, being an essential factor, regulating calcium-phosphate metabolism in the body
Pharmacokinetics	Following the oral administration of a single dose of 0.25 to 1.0 μg of calcitriol, the maximum serum concentrations are reached within 2–6 hours During transport in the blood, 99.9% of calcitriol is bound to alpha-globulins Two metabolic pathways: renal 24-hydroxylase activity with calcitroic acid as the end product, or stepwise hydroxylation of carbon C26 and C23 to produce 1alpha,25R(OH)2-26,23S-lactone D3 The elimination half-life of calcitriol from serum is 3–6 h The pharmacological effect of a single dose is maintained for 3–5 days It is excreted by the gallbladder and undergoes an ileo-hepatic cycle	The onset of activity: 6 hours It reaches its maximum serum concentration after 12 h and 4 h in oral and IV administration, respectively It is transported in the blood together with the vitamin D-binding protein It is rapidly converted to calcitriol in the liver It is excreted mainly in bile and faeces, small amounts with urine

VDR — vitamin D receptor; b.w. — body weight; IV — intravenously

patients with chronic hypoparathyroidism and symptoms of hypocalcaemia and/or albumin-corrected calcium levels < 2.0 mmol/L (< 8 mg/dL) or ionised calcium < 1.0 mmol/L. Treatment with the above-mentioned drugs should also be considered in asymptomatic patients with chronic hypoparathyroidism, in situations where corrected calcium levels are below the lower ranges of their reference values, but > 2.0 mmol/L (>8 mg/dL) or ionised calcium > 1.0 mmol/L, if this could improve their psychophysical well-being. It is recommended that the preparations in question be administered in several divided doses and in such quantities that no symptoms of hypocalcaemia are present and serum calcium concentrations are maintained in the low range of their reference values. The doses of the medications should be increased gradually [23]. The current European recommendations [23] suggest that every patient, despite taking a vitamin D analogue, should also receive 400–800 IU of native vitamin D daily to achieve 25(OH)D concentrations above 20 ng/mL. According to the authors of this elaboration, vitamin D doses may be much higher and should be selected individually so that when monitoring 25(OH)D concentrations the result obtained is within the reference values [24]. A common side effect of treatment is hypercalciuria, and in such cases a reduction in calcium and sodium supply should be considered first, as well as the use of a thiazide diuretic. In patients with hyperphosphataemia and an elevated calcium-phosphate product, it is also worth considering modification of diet and drug dosage. In such cases, an increased calcium supply may result in enhanced phosphate binding in the gastrointestinal tract. Also, magnesium supplementation should not be forgotten in this patient group. The treatment of recombinant PTH agents is reserved for cases refractory to conventional treatment. According to the current guidelines of the European Society of Endocrinology [23], the following vitamin D derivatives and their doses are recommended for the compensation of calcium-phosphate disorders (Tab. 2).

It should be mentioned that when administering supraphysiological doses of native vitamin D, one has to take into account the lack of the expected hypercalcaemic effect and a higher risk of side effects, resulting from an overdose — 25(OH)D concentrations can reach values of 200–400 ng/mL. The current recommendation is to use hypercalcaemic doses of native vitamin D in emergency situations, recognising it as an old treatment option, i.e. when its analogues are not available [23, 25, 26]. As part of the conventional therapy, along with a vitamin D analogue, patients with hypoparathyroidism should receive adequate calcium doses and have any magnesium deficiency compensated for. The equivalent dose of alfacalcidol should be 1.5–2 × the dose of calcitriol used [23, 26, 27] due to the 2-fold higher bioavailability of the latter [26, 28]. Both analogues provide similar efficacy in maintaining normocalcaemia in patients with hypoparathyroidism [26, 28]; however, despite physiological circulating levels of $1\alpha,25(OH)_2D$, up to two-thirds of patients may demonstrate hypercalciuria, which is probably due to the loss of PTH-dependent renal tubular calcium reabsorption [26, 28]. The intention to obtain higher serum calcium concentrations may predispose to the occurrence of hypercalciuria; hence, among other things, it is recommended to keep calcium concentrations in the lower ranges of their reference values. Neither analogue appears to have a stronger effect in reducing elevated phosphate concentrations, which persist despite the increased FGF23 values [26, 27].

Effects of alfacalcidol and calcitriol on bone mineral density and fracture risk

In some randomised clinical trials and meta-analyses, both alfacalcidol and calcitriol have been shown to have significantly increased bone mineral density (BMD) [28], while reducing the incidence of new fractures [16, 21, 30–32]. However, it should be borne in mind that a long-term treatment with vitamin D analogues exposes patients to an increased risk of adverse reactions related to its hypercalcaemic effects, and therefore their use should be restricted to the specific on-label indications [21, 29]. Nuti et al. [29], in their randomised clinical trial with postmenopausal osteoporosis patients, compared the effects of alfacalcidol (1 μg), administered

Table 2. *Dosage of vitamin D and its analogues in hypoparathyroidism*

Substance	Standard dosage	The onset of activity	The end of activity
Calcitriol	0.25–2.0 μg 1–2 × daily	1–2 days	2–3 days
Alfacalcidol	0.5–4.0 μg 1 × daily	1–2 days	5–7 days
Dihydrotachysterol	0.3–1.0 mg 1 × daily	4–7 days	7–21 days
Native vitamin D3 (cholecalciferol) Native vitamin D2 (ergocalciferol)	25,000–200,000 IU daily	10–14 days	14–75 days

IU — international unit

with calcium (1000 mg) on BMD, with those of vitamin D3 (880 IU) combined with calcium (1000 mg). In the alfacalcidol-treated group, lumbar BMD increased by 2.33% from baseline after 12 months and by 2.87% after 18 months, while the vitamin D-treated group demonstrated an increase by only 0.7% at both time points. At the end of the study, serum calcium concentrations were slightly higher in the group receiving alfacalcidol and calcium, compared to the patients receiving native vitamin D and calcium, but the values in the latter case were still within the safety margin. Deng et al. [33], in their meta-analysis of 16 clinical trials involving 1073 patients, showed that both alfacalcidol and calcitriol achieved the greatest efficacy in preventing bone mass loss of the spine and femoral neck in patients taking GCS. The effect of BMD gain, although small, was still significantly greater, compared to that in a calcium therapy in combination with vitamin D. Interestingly enough, native vitamin D in combination with calcium showed higher efficacy in preventing bone mass loss in total hip than its 2 analogues; however, the authors of this paper, bearing in mind the considerable limitations of the studies analysed, e.g. the small size of the groups, are very cautious in drawing conclusions, emphasising the need for further research in this direction [33]. O'Donell et al. [34] evaluated the effects of alfacalcidol and calcitriol on the risk of falls and fall-associated fractures. The authors evaluated 23 randomised clinical trials (2139 participants) and meta-analysed 16 of them. No significant reduction in vertebral fracture risk was demonstrated, based on the combined results of the 13 studies; however, a subgroup analysis showed a significant reduction with alfacalcidol [odds ratio (OR) = 0.50, 95% confidence interval (CI): 0.25–0.98] but not with calcitriol. In addition, the authors found significant reductions in non-vertebral fractures (6 studies, OR = 0.51, 95% CI: 0.30–0.88) and falls (2 studies, OR = 0.66, 95% CI: 0.44–0.98). An increased risk of hypercalcaemia and a trend towards an increased risk of hypercalciuria were also observed [34].

GCSs have been shown to increase 25(OH)D catabolism, but they may also induce body weight gain, which, in turn, is associated with lower 25(OH)D concentrations. Hence the idea that 25-cholecalciferol should be considered as the best analogue for use in obese individuals and, because of its greater hydrophilicity, in individuals with disorders of fat digestion and absorption, e.g. after bariatric surgery [35]. Both of the above-mentioned groups of patients are characterized by an increased risk of fractures [36, 37].

There are many other negative effects of GCS on 25(OH)D concentrations. Dexamethasone has been shown to increase both the renal expression of vitamin D 24-hydroxylase and the expression of 24-hydroxylase mRNA, which degrades vitamin D metabolites, such as 25(OH)D and $1,25(OH)_2D$ [38, 39]. Given the data indicating the inhibition of hepatic 25-hydroxylase, as well as the renal 1-alpha-hydroxylation step, exerted by a GCS therapy, logic would dictate the use of an active vitamin D analogue in patients on this type of therapy as more effective in preventing bone mass loss and fracture incidence [40]; in some clinical trials, active vitamin D analogues have been shown to be more effective than native vitamin D3 in improving bone mineral density (BMD) and reducing the risk of fractures in post-steroid osteoporosis [33, 41], but they were not all unambiguously positive [42, 43]. Richy et al. [43] analysed the efficacy of alfacalcidol and calcitriol in the treatment of primary and GCS-induced osteoporosis, as well as their effects on BMD and fracture risk. A meta-analysis of 17 clinical trials showed a similarly beneficial effect of both analogues on the aspects studied. In a subpopulation of patients not treated with GCS, the analogues significantly reduced the overall incidence and the risk of fractures: RR = 0.52, and both vertebral fractures and in other typical locations (RR 0.53 and 0.34, respectively). No significant difference in responses was observed between the results from the studies in healthy and osteoporotic subjects or according to whether the control group had had the option of calcium supplementation. Based on the data from 5 studies, the effect of treatment with vitamin D analogues on the maintenance of spinal bone mass in patients with GCS-induced osteoporosis was also assessed, and a beneficial effect of the therapy was demonstrated. Only 2 studies looked specifically at the effect of calcitriol on the incidence of vertebral fractures; however, their analysis did not confirm the efficacy of the analogues. The results of other meta-analysis were similar [42].

The literature also contains publications evaluating the efficacy of combination therapy with bisphosphonates and vitamin D analogue. Ringe et al. [22] enrolled 90 patients, diagnosed with osteoporosis (57 women, 33 men), who had randomly been assigned to 3 different therapies (group A: 1 μg of alfacalcidol + 500 mg of calcium daily; group B: 70 mg of alendronate 1 × weekly + 1000 IU vitamin D + 1000 mg of calcium daily; group C: 70 mg of alendronate 1 × weekly + 1 μg of alfacalcidol + 500 mg of calcium daily). At a 2-year follow-up, there was a significantly greater increase in BMD of the lumbar spine and the hip in group C ($p < 0.001$). In addition, the prevalence and number of new fractures in group C was significantly lower. The number of patients with new vertebral fractures after 2 years was 5 in group A, 4 in group B, and one in group C. The prevalence of non-vertebral fractures at 2 years was 4 in group A, 6 in group B, and one in

group C. In addition, the patients treated with bisphosphonate and alfacalcidol revealed a lower prevalence of falls and a faster reduction in the severity of back pain. Jing et al. [44] also demonstrated beneficial effects of a combination therapy with calcitriol, the vitamin D analogue, and bisphosphonates in postmenopausal women with osteoporosis, not only in terms of BMD, but also with regards to pain reduction and improved quality of life. One of the largest studies of a combination therapy with a vitamin D derivative and an antiresorptive drug was conducted by Orimo *et al.* [45], who included more than 2000 patients and showed that the combination of alfacalcidol and alendronate had not been effective in preventing vertebral fractures. However, a subgroup analysis showed that it had been more effective in preventing fractures in patients with severe spinal deformities, multiple previous vertebral fractures and in preventing non-vertebral fractures [45]. Shao *et al.* [46] provided even more convincing evidence, publishing the results of their meta-analysis and including data from 13 randomised clinical trials with more than 3500 patients. Nine studies were conducted in Japan, 2 in Germany, one in China, and one in the Netherlands. The combination of alendronate and alfacalcidol was shown to be significantly more effective in preventing bone fractures than alendronate alone (OR = 0.53, 95% CI: 0.19–0.95) or alfacalcidol (OR = 0.25, 95% CI: 0.08–0.49) in monotherapy [46]. Another study involving patients with osteoporosis of both sexes showed that alfacalcidol, in combination with alendronate, had statistically significantly better efficacy in reducing the total number of new vertebral or non-vertebral fractures, compared to native vitamin D in combination with either a bisphosphonate alone or alfacalcidol without a bisphosphonate. That study also showed that 80% of the patients receiving alfacalcidol in combination with alendronate had not been suffering from back pain after 2 years, compared to 30% of those taking alendronate with native vitamin D ($p < 0.003$) [47].

Most studies on denosumab have been conducted in combination with native vitamin D and calcium, with only a few comparing its efficacy in combination with vitamin D analogues. In a 12-month retrospective study, the effects of denosumab in combination with alfacalcidol and of denosumab with native vitamin D were compared [48]. Postmenopausal women with mean age > 75 years received subcutaneously 60 mg denosumab every 6 months in combination with orally administered cholecalciferol (10 μg) and calcium (610 mg/day) (n = 60) or with orally administered alfacalcidol (0.25–1.0 μg/day) and calcium (0–260 mg/day) (n = 67). The therapy was selected at the individual discretion of each doctor [48]. Both groups experienced a significant increase in BMD at the lumbar spine and the entire hip, which was evident after 6 months; however, only the alfacalcidol-treated group experienced a significant increase in BMD of the femoral neck, $p < 0.001$, both from baseline and *vs.* the group receiving standard vitamin D after 6 and 12 months. There was also a significant increase in BMD in the distal forearm in the alfacalcidol group, both from baseline and compared to the native vitamin D group after 12 months ($p < 0.1$) [48].

Table 3. ***Data on the type and incidence of symptoms and adverse events associated with the use of both vitamin D analogues [12, 19, 46]***

Classification of systems and organs (MedDRA)	A vitamin D derivative	The incidence of adverse reactions				
		Very high (≥ 1/10)	High (≥ 1/100 to < 1/10)	Medium-high (≥ 1/1 000 to < 1/100)	Low (≥ 1/10 000 to < 1/1 000)	The incidence is unknown (it cannot be determined from available data)
Immunological system disorders	Calcitriol				Severe allergic reactions to peanut oil	Hypersensitivity, urticaria
	Alfacalcidol					Hypersensitivity
Metabolic and nutritional disorders	Calcitriol			Decreased appetite		Polydipsia, dehydration, body weight loss
	Alfacalcidol					
Psychic disorders	Calcitriol					Apathy, psychic disorders
	Alfacalcidol					Confusion
Nervous system disorders	Calcitriol		Headache			Muscle weakness, sensory disturbances, drowsiness
	Alfacalcidol			Headaches	Dizziness	

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Cardiac disorders	Calcitriol					Arrhythmia
	Alfacalcidol					Arrhythmia
Gastric disorders	Calcitriol		Abdominal pain, nausea	Vomiting		Constipation, paralytic bowel obstruction
	Alfacalcidol		Abdominal pain, discomfort in the abdomen	Diarrhoea, vomiting, constipation, nausea		Dryness in the oral cavity, increased thirst, irritation of mucous membranes including gastric mucosa, metallic taste in the mouth
Skin and subcutaneous tissue disorders	Calcitriol		Rash			Erythema, pruritus
	Alfacalcidol		Rash, pruritus			Urticaria
Musculoskeletal and connective tissue disorders	Calcitriol					Growth retardation
	Alfacalcidol			Muscle pains		Bone pains
Kidney and urinary tract disorders	Calcitriol		Urinary tract infection			Polyuria, nycturia, hypercalciuria
	Alfacalcidol		Hypercalciuria	Nephrolithiasis, nephrocalcinosis		Deterioration of kidney function
General disorders and conditions at administration site	Calcitriol					Nephrocalcinosis, ectopic calcifications fever, increased thirst
	Alfacalcidol			Ectopic calcifications fatigue Asthenia		
Diagnostic examinations	Calcitriol	Hypercalcaemia		Elevated concentration of blood creatinine		
	Alfacalcidol		Hypercalcaemia, hyperphosphataemia			

MedDRA — Medical Dictionary for Regulatory Activities

Safety of use of alfacalcidol and calcitriol

No clinical trial results were found in the literature that would directly have addressed the tolerability of the 2 drugs and the safety of their use in the context of a comparative analysis. Table 3 brings together the information on the type and incidence of symptoms and adverse events associated with the use of the 2 vitamin D analogues (Tab. 3) [12, 19, 49]. The prevalence of individual symptoms may vary slightly, depending on the manufacturer of the preparation.

Summary

Both alfacalcidol and calcitriol can interchangeably be used in everyday endocrinology practice, taking into account their drug product characteristics and the current recommendations of scientific societies. However, certain differences regarding the bioavailability and potency of the 2 drugs have to be borne in mind, hence the need for careful dose adjustments when switching from one drug to the other.

Conflicts of interest

All authors certify that they have no financial interests such as employment, stock ownership, honoraria, paid expert testimony, as well as any personal relationships, academic competition, and intellectual passion, which may inappropriately influence their actions.
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All authors have had full access to all the data in the study (if applicable) and thereby accept full responsibility for the integrity of the data and the accuracy of the data analysis.

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