Alfacalcidol

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

EMLc | ATC codes: A11CC03

Indication	Disorders of vitamin D metabolism or transport ICD11 code: 5C63.2
INN	Alfacalcidol
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Liquid:** 2 µg per mL **Oral > Solid > capsule:** 0.25 µg ; 1 µg
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Alfacalcidol
DrugBank	Alfacalcidol

Expert Committee recommendation

The Expert Committee noted that the application referred to three guidelines that conditionally recommended vitamin D analogues for the treatment of people with chronic kidney disease, hypophosphataemic rickets and hypoparathyroidism, but did not elaborate on any of the evidence underpinning the guideline recommendations. The Committee noted a recent systematic review identified during the application review process that suggested that calcitriol and alfacalcidol might result in benefits for people with chronic kidney disease in terms of some surrogate outcomes for clinical benefit such as fewer fractures. Overall, the Committee noted that the evidence base was uncertain due to the risk of bias, indirectness when assessing patient-important outcomes, inconsistencies and imprecision. The Committee considered that the limited likelihood of influencing important clinical outcomes was potentially outweighed by the risks associated with the use of alfacalcidol and calcitriol, such as hypercalciuria, decreased renal function and cardiovascular risk. The Expert Committee therefore did not recommend the inclusion of alfacalcidol and calcitriol on the complementary list of the EML and EMLc for the proposed indications of hypoparathyroidism, hypophosphataemic rickets, hypocalcaemic vitamin D dependent/resistant rickets, neonatal hypocalcaemia, chronic kidney disease or other disorders of vitamin D metabolism or transport.

Background

Alfacalcidol and calcitriol have not previously been considered for inclusion in the Model Lists for management of

disorders of bone and calcium metabolism, or any other indication. The Model Lists currently include vitamin D as cholecalciferol and ergocalciferol for the management of vitamin D deficiency.

Public health relevance

Vitamin D analogues are used in situations where endogenous vitamin D cannot be produced, or exogenous 25 hydroxyvitamin D (25(OH)D) cannot be absorbed or converted to active vitamin D in the kidney and liver. These situations include chronic kidney disease, hypophosphataemic rickets (including X-linked) and hypoparathyroidism (1). Data from the Global Burden of Disease study indicate that the global prevalence of chronic kidney disease was estimated to be almost 700 million in 2019 (2). The prevalence varies between countries, with a large burden in low- and middle-income countries. X-linked hypophosphataemia has a reported incidence of 3.9 per 100 000 live births and a prevalence of 4.8 per 100 000 population (all ages) (3). Hypoparathyroidism has a number of potential causes and overall population prevalence data are difficult to obtain. A study in Denmark suggested a population prevalence (all ages) for surgical and non-surgical hypoparathyroidism of 22 per 100 000 and 2.3 per 100 000, respectively (4–6). Incidence rates for some of the conditions that cause hypoparathyroidism in childhood are available. The annual birth incidence of 22q11 deletion syndrome has been reported as 14 per 100 000 in a study in Sweden (7), and 22 per 100 000 in a study in Australia (8).

Benefits

The application stated that treatment for the proposed indications with vitamin D analogues is long-standing and well established. Their use is recommended in guidelines for management of chronic kidney disease (9), hypophosphataemic rickets (10,11) and hypoparathyroidism (12). Most recent clinical trials compare other medications with vitamin D analogues as the gold standard. As such, no recent placebo-controlled clinical trials of these medicines are available. A randomized, open-label trial compared alfacalcidol and calcitriol for the management of patients with hypoparathyroidism. Patients with hypoparathyroidism with optimal calcaemic control on alfacalcidol were randomized to continue alfacalcidol (n = 20) or switch to calcitriol (n = 25) at half the ongoing alfacalcidol dose for 6 months. No significant differences were observed between the alfacalcidol and calcitriol arms from baseline to 6 months for the main outcomes of: mean serum phosphate level (5.0 mg/L versus 4.9 mg/dL, P = 0.75); proportion of patients with hyperphosphataemia (75% versus 80%, P = 0.73); 24-hour urine calcium-to-creatinine ratio (0.23 versus 0.28, P = 0.26); proportion of patients with hypercalciuria (65% versus 68%, P = 0.99); mean 24-hour urinary calcium excretion (198 mg versus 260 mg, P = 0.08); or mean 24-hour urinary sodium excretion (85 mmol versus 95 mmol, P = 0.41) (13).

Harms

The application reported that, to date, alfacalcidol and calcitriol have large total patient exposure. The risks associated with treatment relate directly to the appropriateness of the dosage. No side-effects linked to intolerance to the medicines themselves are known. The most common risks associated with treatment include renal nephrocalcinosis and hypercalcaemia (in case of excessive dosage) or hypocalcaemia (in case of insufficient dosage), the risk of which varies by indication. Monitoring of serum and urine chemistry is recommended.

Cost / cost effectiveness

No cost–effectiveness data were presented in the application. Table 23 (refer TRS 1049) shows the prices reported in the application for alfacalcidol and calcitriol.

WHO guidelines

WHO guidelines for the management of disorders of bone and calcium metabolism are not currently available.

Availability

Alfacalcidol and calcitriol are reported to be available globally, with generic versions available in many countries.

Other considerations

A 2021 systematic review and meta-analysis of 22 randomized trials that investigated different forms of vitamin D supplementation in patients with chronic kidney disease was identified during the application review process (14). Calcitriol and vitamin D analogues (alfacalcidol and paricalcitol) were associated with a reduction in parathyroid hormone concentration compared with vitamin D2 or D3 (mean difference –14.69 pg/mL, 95% confidence interval –36.29 to 6.90 pg/mL; four randomized controlled trials, 274 participants) and increase in fibroblast growth factor 23 (three randomized controlled trials, meta-analysis not performed), both indirect measures of important clinical outcomes, for example, fractures, cardiovascular disease risk and mortality. Inconsistent results for serum calcium and serum phosphate concentrations were noted. However, the evidence was considered uncertain because of the risk of bias, indirectness, inconsistencies and imprecision.

1. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014;21(3):319–29.
2. Global Burden of Disease database [internet]. Seattle, WA: Institute for Health Metrics and Evaluation; 2019 (https://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
3. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019;15(7):435–55.
4. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. J Bone Miner Res. 2013;28(11):2277–85.
5. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism – risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res. 2014;29(11):2504–10.
6. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. The epidemiology of nonsurgical hypoparathyroidism in denmark: a nationwide case finding study. J Bone Miner Res. 2015;30(9):1738–44.
7. Oskarsdottir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Arch Dis Child. 2004;89(2):148–51.
8. Hui L, Poulton A, Kluckow E, Lindquist A, Hutchinson B, Pertile MD, et al. A minimum estimate of the prevalence of 22q11 deletion syndrome and other chromosome abnormalities in a combined prenatal and postnatal cohort. Hum Reprod. 2020;35(3):694–704.
9. Yuen NK, Ananthakrishnan S, Campbell MJ. Hyperparathyroidism of renal disease. Perm J. 2016;20(3):15–127.
10. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3(1):R13–30.
11. Trombetti A, Al-Daghri N, Brandi ML, Cannata-Andia JB, Cavalier E, Chandran M, et al. Interdisciplinary management of FGF23-related phosphate wasting syndromes: a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia. Nat Rev Endocrinol. 2022;18(6):366–84.
12. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101(6):2273–83.
13. Saha S, Sreenivas V, Goswami R. Alfacalcidol vs calcitriol in the management of patient with hypoparathyroidism: a randomized controlled trial. J Clin Endocrinol Metab. 2021;106(7):2092–102.
14. Christodoulou M, Aspray TJ, Schoenmakers I. Vitamin D supplementation for patients with chronic kidney disease: a systematic review and meta-analyses of trials investigating the response to supplementation and an overview of guidelines. Calcif Tissue Int. 2021;109(2):157–78.

