Application for Inclusion of Calcitriol (1,25-dihydroxy-cholecaliferol) and alfacalcidol (1α-calcidol) in the WHO Model List of Essential Medicines for adults and for children (April 2023)

1. **Title page:**

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To:
24th WHO Expert Committee on the e Selection and use of Essential medicines,
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2. Summary Statement of the Proposal for inclusion, change or deletion

The proposal is made in support of inclusion of 1,25-dihydroxy-cholecalciferol (Calcitriol) and alfalcidol on the complementary list of the EML and EMLc, for the management of relevant disorders of bone and calcium metabolism, in adults and in children.

Context

– Non-communicable Diseases

In 2015 the UN convened to declare a post-Millenium Declaration (MD) development agenda that contains 17 sustainable Development Goals (SDGs) and importantly NCDs are now an SDG target (1).

-Capacity in Endocrinology

Endocrinology is a subspecialty of internal medicine and of pediatrics that focuses on the diagnosis and treatment of adults and children with diseases of the endocrine system. These conditions are part of the non-communicable diseases (NCD) group. Capacity in endocrinology is increasing worldwide and endocrinologists are now in a situation where many endocrine conditions, previously unrecognized by health professionals in low- and middle-income countries (LMICs) are diagnosed in a timely fashion. This is true not only in adults but also in children. Indeed, over the past 15 years, thanks to training programs developed by a number of regional Pediatric Endocrine societies, supported by Pediatric Endocrine Societies affiliated with the International Consortium of Pediatric Endocrinology & Diabetes Societies (ICPE), capacity in Pediatric Endocrinology has increased considerably. However, access to medicines that can save lives or prevent irreversible complications and that have been available in high income countries (HICs) for decades remains poor.

The need for Vitamin D analogues

Vitamin D analogues are medicines that decrease mortality and morbidity in situations where endogenous Vitamin D cannot be produced or exogenous 25-(OH) vitamin D absorbed or converted. This includes, but is not limited to, chronic kidney disease, hypophosphatemic rickets (including X-linked) and hypoparathyroidism. In order to be active, vitamin D needs to undergo 1 alpha hydroxylation (in the kidney) and 25 hydroxylation (in the liver). Vitamin D analogues used in clinical practice include calcitriol (1,25-dihydroxy-cholecaliferol) and alfacalcidol (1α-calcidol) (2).

Chronic kidney disease

Chronic kidney disease is a very common condition that can be due to a variety of causes, including hypertension and diabetes. It is highly prevalent (see below). As it progresses, the kidney becomes unable to perform 1 alpha hydroxylation that is required for normal vitamin D action. Insufficient Vitamin D action in patients with chronic kidney diseases leads to impaired calcium metabolism and bone disease (3). These patients are in need of analogues of vitamin D that are 1 alpha hydroxylated (either alfacalcidol or calcitriol)

Hypoparathyroidism, hypophosphatemic rickets and genetic causes of abnormal calcium metabolism

X-linked hypophosphatemic rickets is a genetic condition involving the PHEX gene and abnormal fibroblast growth factor 23 (FGF-23) regulation (4). It leads to phosphate wasting and therefore rickets. Management involves careful balancing of phosphate therapy (**using frequent dosing of soluble phosphate, see other application to the 24th WHO Expert Committee**) and vitamin D analogues, in the form of calcitriol or 1-alfacalcidol. Inadequate balancing of these two components leads to failure to heal the rickets, or can lead to calcium deposition in the kidneys and impaired renal function. For young children a liquid form of an active vitamin D compound is essential (currently this is 1-alfacalcidol) while for older patients access to capsules of calcitriol or 1-alfacalcidol is essential for dose adjustments.

Vitamin D dependent rickets represents a group of conditions with abnormalities in either metabolism of vitamin D or in the vitamin D receptor, leading to rickets or abnormal calcium, homeostasis. Several of these conditions are autosomal recessive and as such consanguinity is an important factor to consider (5).

Hypoparathyroidism has a wide range of causes, which frequently differ in children and adults. While hypoparathyroidism following neck surgery (the commonest cause in adults) and auto-immune hypoparathyroidism both occur, in children it is more commonly a consequence of syndromes (e.g. the 22q11 microdeletion syndrome), caused by genetic abnormalities in the calcium-sensing receptor, or a component of a genetically determined broader autoimmune phenotype (one of the polyglandular autoimmune syndromes). These conditions commonly lead to hypocalcemic seizures or may be picked up following diagnosis of a syndrome or of an affected family member. In all of these conditions careful treatment with vitamin D analogues is required to maintain serum calcium levels at a range that prevents seizures but minimises any risk of calcium deposition in the renal tract (nephrocalcinosis or renal tract stones), which over time will lead to chronic renal failure (6). Active vitamin D analogues, including a liquid preparation, are an essential requirement for treating these conditions (often in association with calcium supplementation, which is presently included under section 27 of the EML), with the key goal to maintain adequate serum calcium without over-treatment.

3. Consultation with WHO Technical departments

No WHO department was consulted, However, in 2019, WHO published a detailed document on “Nutritional rickets: a review of disease burden, causes, diagnosis, prevention and treatment” (7). To our knowledge, in contrast to the most common form of rickets (Vit D deficient rickets), no WHO department has proposed guidelines for conditions associated with resistance to Vitamin D. Another aspect is that 1,25-dihydroxy-cholecalciferol (Calcitriol) or 1α-Calcidol are not included in the document. It is clear that the proposed medicines **are not and should not be** a long-term approach for the management of Vit D deficient rickets. However, they are commonly used for a few days for the emergency management of severe hypocalcemia (in addition to IV Calcium as recommended in the WHO document) associated with Vit D deficient rickets because of their rapid onset of action, until supplementation in Vit D becomes effective (8).

4. Other Organizations Consulted and/or supporting the Submission

This submission is part of a larger project by a group of endocrinologists with worldwide representation who met regularly for 12 months (2020-2021) with the goal of performing an in-depth review of the essential medicines included in Section 18. of the EML and the EMLc (“Medicines for endocrines disorders”). The group included both adult and pediatric endocrinologists: Drs. Chanoine (Canada) and Molitch (USA) (co-Chairs) and Drs. von Oettingen (Canada), Villarroel (Bolivia), Kalra (India), Paulose (India), Abodo (Ivory Coast), Ramaiya (Tanzania), Donaghue (Australia), Junfen Fu (China) and de Beaufort (Luxembourg). In addition, we worked with economists (Drs. Ewen and Beran from Switzerland), pharmacists (Drs. Kavanagh and Gray from UK and Karekezi from Kenya) and a dietitian (Dr. Besançon from Mali). This application is led by Global Pediatric Endocrinology and Diabetes (GPED) and the International Society of Endocrinology (ISE).

The first author (Pr E Wiltshire) of the present submission is president of the International Consortium for Pediatric Endocrinology (ICPE). The submission was discussed and approved by the representatives of each regional society for Pediatric Endocrinology that ICPE represents (see letter of support #a).

Co-author Pr JP Chanoine is Secretary General of Global Pediatric Endocrinology and Diabetes (GPED). GPED is a non-profit organisation founded in 2010 and incorporated in Canada. It is endorsed by all regional pediatric endocrine societies (see www.globalpedendo.org) and is a founding member of ICPE. The mission of GPED is “to

improve the care of children living in developing countries and presenting with endocrine disorders or with diabetes". One of the specific objectives of GPED is to improve access to essential medicines for Pediatric Endocrine diseases in LMICs (see letter of support #b). Dr Chanoine has received the support from GPED.

Co-author Pr M Molitch is an adult endocrinologist. He has secured the support of the International Society for Endocrinology (ISE) (see letter of support #c).

The Endocrine Society is an international organization of over 18,000 endocrinologists that includes clinicians and basic scientists. It promotes breakthroughs in scientific discovery and medical care through publishing in its peer-reviewed journals, hosting an annual scientific meeting, creating resources and educational materials to help clinicians and investigators accelerate the pace of scientific discovery and translation of the latest science into clinical care, advocating for appropriate support and policies that benefit healthcare providers and patients, and educating the public about hormones and the roles that endocrine scientists and clinicians play in achieving optimal public health. The Endocrine Society publishes Clinical Guidelines for clinical care (Letter of support #d)

Finally, this submission is supported by the XLH network (letter of support #e). The XLH network is a worldwide patient support organization for people living and dealing with X-linked hypophosphatemia (XLH) (https://www.xlhnetwork.org/). Importantly, the letter of support from the XLH network highlights the importance of having both phosphorus and alfacalcidol/calcitriol added to the EML/EMLc because both medicines are an integral part of the treatment of X-linked hypophosphatemic rickets.

5. Key Information for the Proposed Medicines

International non-proprietary name (INN) of the proposed Medicines

1. Alfacalcidol
2. Calcitriol

Anatomic therapeutic chemical (ATC) code of the proposed medicine

1. Alfacalcidol - A11CC03
2. Calcitriol - A11CC04

Dosage form(s) and strength(s) of the proposed Medicines

1. Alfacalcidol-
    a) Liquid 2 micrograms/ml
    b) Capsules 0.25 micrograms/capsule
    c) Capsules 1 microgram/capsule
2. Calcitriol
    a) Capsules 0.25 micrograms/capsule
    b) Capsules 0.5 microgram/capsule

Indications

1. 5A50 Hypoparathyroidism including: 1) 5A50.0Y Other specified hypoparathyroidism, 2) 5A50.1 Pseudohypoparathyroidism; 3) 5A50.03 Autoimmune hypoparathyroidism; 4) LD44.N0 CATCH 22 phenotype
2. 5C63.22 Hypophosphataemic rickets
3. 5C63.2Y Other specified disorders of vitamin D metabolism or transport
4. 5C63.20 Hypocalcaemic vitamin D dependent rickets (emergency treatment)
5. 5C63.21 Hypocalcaemic vitamin D resistant rickets
6. KB61.2 Neonatal hypocalcaemia (emergency treatment)
7. GB61 Chronic kidney disease

6. Proposal for an individual Medicine or Representative of a Pharmacological class/therapeutic group

We submit the inclusion of alfacalcidol and calcitriol as two different medicines used for the management of the disorders noted above. They are often, but not always, interchangeable. Indeed, there are some differences that impact their use in clinical practice. Calcitriol (1,25-dihydroxycholecalciferol) is the active form of the medication that acts on the Vitamin D receptor. Alfacalcidol (1-hydroxycholecalciferol) must have a hydroxyl group added to the 25 position to be activated to calcitriol and work on the vitamin D receptor. In patients with liver disease, in patients receiving a variety of other medications that are inhibitors or inducers of 25-hydroxylase (of which there are a large number) or in patients with 25 hydroxylase deficiency (a rare recessive condition), calcitriol is the safer medication to use. Currently only alfacalcidol is available as a liquid medication. Of note standard vitamin D preparations (used in treatment for vitamin D deficiency including vitamin D deficiency Rickets) cannot be used for the above indications, as they lead to either over- or under treatment and serious complications (2).

Please note that cholecalciferol and ergocalciferol are both included in the EML as treatments for vitamin D deficiency (including vitamin D deficiency rickets). However, neither of these is suitable for treatment of the indications listed above as they are associated either with the inability to treat the above indications, or with over-treatment, leading to nephrocalcinosis and chronic renal failure. We can also not submit these two medicines as a "class". Indeed, there is an increasing number of Vitamin D analogs (9). Most are in development or used for the management of other conditions are not presently relevant to this application.

<u>Suggested wording</u>

Alfacalcidol and calcitriol are available as capsules. Only alfacalcidol is available as a liquid form, which is required for young children (2 micrograms/ml)

Vitamin D (cholecalciferol and ergocalciferol) are already included in section 27. VITAMINS AND MINERALS of the EML and EMLc for the prevention of rickets. However, the present submission focuses on Vitamin D analogues (Alfacalcidol and calcitriol) as essential medicines to be used in medical conditions where endogenous Vitamin D cannot be produced or exogenous 25-(OH) vitamin D absorbed or converted. As such, we suggest, similar to phosphorus (see other submission to the EML committee) that alfacalcidol and calcitriol be part of a new subsection on "diseases of bone and calcium metabolism" within section 18. MEDICINES FOR ENDOCRINE DISORDERS.

The conditions described in this submission are usually managed by a specialist (pediatric or adult endocrinologist). Thus, we propose that alfacalcidol and calcitriol be included in the complementary list.

18. MEDICINES FOR ENDOCRINE DISORDERS	
18.8 Diseases of bone and calcium metabolism	
Complementary list	
alfacalcidol	Capsules: 0.25 mcg; 1 mcg Oral liquid 2 mcg/ml
calcitriol	Capsule: 0.25 mcg; 0.5 mcg

7. Information supporting the public health relevance

Epidemiology

The prevalence of chronic kidney disease varies from country to country and reflects in part the success of managing two important causes of the disease: diabetes and hypertension. Recent estimates suggest that chronic kidney disease affects 800 million people in the world. Chronic kidney disease represents an especially large burden in LMICs. In India, prevalence estimates vary from 5.8% (in rural areas) to 28% (in urban areas) (10). Although not all patients require vitamin D analogues, they need to be prescribed more and more often as the kidney function deteriorates (11).

X-linked hypophosphatemic rickets has a birth incidence of 3.9/100,000 live births (12). Population prevalence data for hypoparathyroidism are difficult to obtain, as there are a large number of causes. However a study in Denmark suggested population prevalence (including adults and children) for surgical and non-surgical hypoparathyroidism at 22/100 000 and 2.3/100 000, respectively (13-15). Incidence rates for a number of the conditions that cause hypoparathyroidism in childhood are available – for example the annual birth incidence of the 22q11 deletion syndrome in Sweden was 14/100,000 (16) and in Victoria, Australia 22/100,000 births, making it one of the most common chromosomal disorders (17). Overall, these means a large number of children worldwide are affected by these conditions.

Target Population

The target population is adults and children affected by the conditions listed above under “indications”.

8. Treatment Details

Dosage Regimen and duration of treatment

Treatment regimens for the above indications need to be individualised, with dose adjustments happening frequently, particularly in children who are still growing. In general treatment for the above indications will be lifelong (Indications 1, 2, 3, 5, 7 under section 5 above). Doses vary by indication and age. In children, doses generally range from 20–30 ng/kg for calcitriol or 30–50 ng/kg for alfcalcidol. In adults, doses generally range from 0.25-1.0 mcg for calcitriol and 0.5 -2.5 mcg for alfacalcidol (18). Doses are adapted to the specific parameters of the clinical context, in particular calcemia.

Requirements to ensure appropriate use of the medicine(s)

Treatment would need to be supervised by a paediatric endocrinologist or by an adult endocrinologist. Frequent dosage adjustments are required, including access to accurate growth assessment and access to appropriate biochemical monitoring. The latter includes the ability to measure serum calcium, serum phosphate, serum alkaline phosphatases (ALP) and ideally serum parathyroid hormone, together with assessment of urinary calcium excretion. Total and ionized calcium, phosphate and ALP are all on the WHO Essential In Vitro Diagnostics List (19) and PTH is being considered for the 4th edition of the EDL. Access to renal ultrasound for monitoring renal calcium accumulation is also important (although may not be essential in areas where access to radiology is difficult).

Recommendations in existing WHO guidelines

Not found

Recommendations in other current clinical guidelines

The proposed inclusions are used for a variety of indications. However there are specific guidelines for the management of each individual indication for which these medications are necessary: chronic kidney disease (3), hypophosphatemic rickets (4, 20) and for management of hypoparathyroidism (6).

9. Review of Benefits: Summary of Evidence of Comparative Effectiveness

Treatment for the indications listed with vitamin D analogues is long-standing and well established. They are included in guidelines for management of these conditions referred in this submission. Most recent clinical trials involve other medications being compared with vitamin D analogs as the gold standard. As such, there are no recent placebo controlled clinical trials of these agents (which would be unethical). A recent study compared calcitriol with alfacalcidol and did not show significant differences between them (21) in relation to restoration of normal serum calcium, frequency of hyperphosphatemia and calcium excretion.

10. Review of harms and toxicity: Summary of evidence of comparative safety

These medications are well established in treatment for the noted indications, with a very large total patient exposure to date. The risks associated with treatment relate directly to the appropriateness of the dosage. To our knowledge, there are no side effects linked to intolerance to the medicine itself. Most common risks include renal nephrocalcinosis and hypercalcemia (in case of excessive dosage) or hypocalcemia (in case of insufficient dosage), the risk for which varies by indication. Both of these complications can be prevented with appropriate monitoring, aiming for a serum calcium concentration that is appropriate for the specific condition and monitoring both serum and urine chemistry. The data regarding potential toxicity are summarised in the clinical guidelines and reviews noted above.

11. Summary of Available Data on Comparative Cost-Effectiveness

It is important to know that generic versions of these medicines are now available in many countries. The prices below are for generic, when available.

Examples of cost (**in USD**):

1. New Zealand: Current cost for alfacalcidol in New Zealand is 0.26 cents per 0.25 mcg capsule **(=0.16 USD)**, $NZ 0.88 per one microgram capsule **(=0.55 USD)** and $NZ1.5 per mcg for the liquid formulation **(=0.95 USD)**. For calcitriol to costs are $NZ0.78 per 0.25 mcg capsule **(=0.49 USD)** and $1.37 per 0.5 mcg capsule **(=0.86 USD)**. This works out to between $NZ1 **(=0.63 USD)** and $NZ2 **(=1.26 USD)** for average daily dosing.
2. UK: The current published drug tariff cost for alfacalcidol liquid in the United Kingdom is £0.16 per 0.25microgram capsule **(=0.19 USD)**, £0.33 per 0.5 microgram capsule **(=0.40 USD)** and £0.16 per 1microgram capsule **(=0.19 USD)** and £1.06 per microgram of the liquid **(=1.28 USD)**. For calcitriol the cost is £0.26 per 0.25microgram capsule **(=0.31 USD)** and £0.74 per 0.5microgram capsule **(=0.90 USD)**.
3. India: Alphacalcidol (0.25 mcg): 6.83-10.3 INR **(= 0.08-0.13 USD)**
   Calcitriol (0.25 mcg): 28.4 INR **(= 0.35 USD)**
4. Argentina: Calcitriol 0.25 mcg = **0.30 USD** per tablet. There is no alfacalcidol
5. Mexico: Calcitriol 0.25mcg tablets: 5.5 pesos **(= 0.28 USD**); Alfa calcidiol 1mcg Tablet 24 pesos **(= 1.24 USD**)
6. South Africa: Calcitriol (strength unknown) 12.11 ZAR **(=0.71 USD)**; Alfacalcidol 0.25 mcg 8.31 ZAR **(= 0.49 USD)**, 1mcg 24.69 ZAR **(=1.46 USD)**

12. Regulatory status, market availability and Pharmacopoieal Standards

These medications are approved for use in many jurisdictions and are generally available

U.S. Food and Drug Administration (FDA):

Alfacalcidol and calcitriol are on the approved product list (Orange book).

European Medicines Agency (EMA):

Alfacalcidol and calcitriol are approved for use in the EMA regions and for inclusion on the list of nationally approved medicinal products.

Australian Government, Department of Health, Therapeutic Good Administration:

Alfacalcidol and calcitriol

Health Canada:

Alfacalcidol and calcitriol are on the drug product list of approved medicines.

Japanese Pharmaceuticals and Medical Devices Agency:

Alfacalcidol and calcitriol are is included in the PMDA list of approved medicines.

Availability of pharmacopoeial standards

(British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Alfacalcidol

BP	IP	USP	EP
Yes	No	No	Yes

Calcitriol

BP	IP	USP	EP
Yes	No	Yes	Yes

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