




A Health Technology Assessment Based on Chinese Guideline: Active Vitamin D and Its Analogs in the Treatment of Osteoporosis

Siyong Huang , Jiabao Li, Xiao Hu , Jisheng Chen 

Key Specialty of Clinical Pharmacy, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, People's Republic of China

Correspondence: Jisheng Chen, Key Specialty of Clinical Pharmacy, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangdong, 510080, People's Republic of China, Tel +86 20-87622305, Fax +86 20-61321967, Email cjslym@163.com

Objective: To quantitatively assess all dosage forms of three active vitamin D and its analogs, namely, calcitriol, alfacalcidol, and eldcalcitol, to provide a basis for the selection of active vitamin D and its analogs in hospitals.

Methods: In this study, three active vitamin D and its analogs were evaluated by quantitative scoring in five dimensions, including pharmaceutical properties (28 points), efficacy (27 points), safety (25 points), economy (10 points), and other attributes (10 points).

Results: The final scores of quantitative assessment for the selection of alfacalcidol soft capsules, calcitriol soft capsules I, calcitriol soft capsules II, alfacalcidol tablets, alfacalcidol capsules, alfacalcidol oral drops, calcitriol injection, and eldcalcitol soft capsules were 73.17, 72.06, 71.52, 71.29, 69.62, 68.86, 65.60, 64.05 points.

Conclusion: Based on the scoring results, alfacalcidol soft capsules, calcitriol soft capsules I, calcitriol soft capsules II, alfacalcidol tablets can be entered into the medication list of medical institutions as strongly recommended drugs. This study offers guidance on selecting and using active vitamin D and its analogs in hospitals, with consideration for the patient's needs.

Keywords: osteoporosis, active vitamin D, calcitriol, alfacalcidol, eldcalcitol, hospital health technology assessment

Introduction

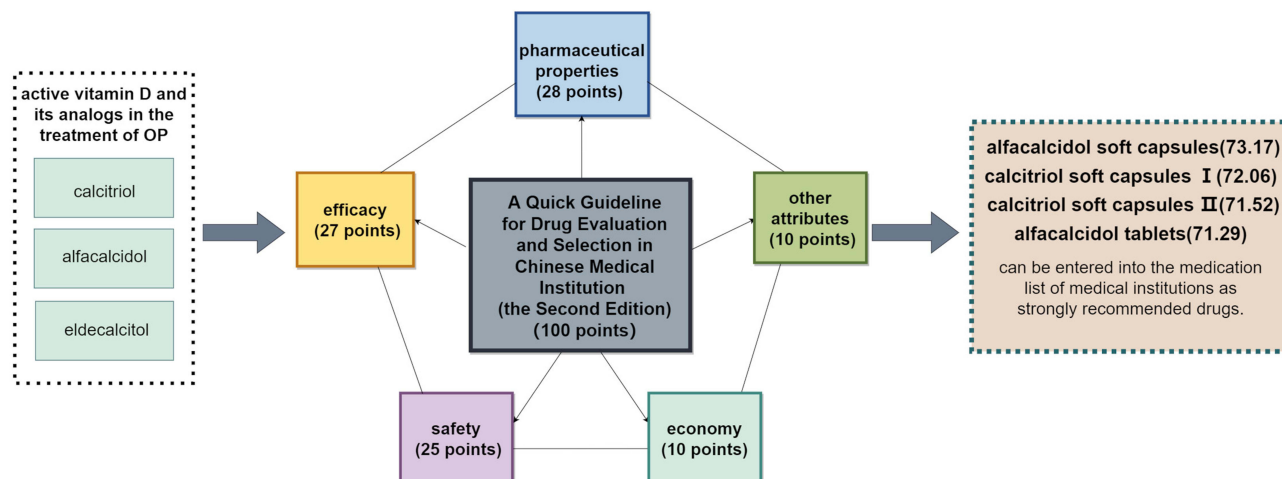
Osteoporosis (OP) is a systemic bone disease characterized by low bone mass and damage to the microstructure of bone tissue, leading to increased bone fragility and susceptibility to fracture.¹ Like osteoarthritis, the incidence of osteoporosis increases with age, and it is more common in women than in men, causing a burden to society.^{2,3} Currently, active vitamin D and its analogs (hereinafter referred to as active vitamin D) are marketed in China for treating OP, including calcitriol, alfacalcidol, and eldcalcitol. Active vitamin D has been shown to increase bone mineral density and reduce the risk of falls and lower fractures.⁴⁻⁷ Evidence-based pharmacology has shown differences in safety and efficacy of active vitamin D with different molecular structures. Select the appropriate active vitamin D can play a vital role in the condition of patients with OP and reduce the economic burden. But how to scientifically evaluate and select active vitamin D is an urgent issue for medical institutions. In 2023, China issued "A Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institution (the Second Edition)" (hereinafter referred to as "The Second Edition").⁸ Compared with the first edition, the guidelines made scientific and reasonable adjustments to the weight of the five dimensions of rapid selection of drugs for hospitals. Based on "The Second Edition", this study quantitatively evaluates the active vitamin D through five dimensions, aiming to provide a basis for the selection of drugs for hospitals and can be a reference for medical decision-making in other regions.

Materials and Methods

Evaluation Basis

This study is based on "The Second Edition", which adopts the Mini-health technology assessment (Mini-HTA) combined with the system of objectified judgment analysis(SOJA). The evaluation dimensions and weights were

Graphical Abstract



determined by the guideline guidance group and the expert group through the Delphi method.⁸ In addition, compared with the first edition of this guideline, “The Second Edition” has revised and refined the evaluation indicators, so that the quantitative scoring can better reflect the priority of drugs in medical institutions, and the scoring items are more detailed, clear, and easy to operate. “The Second Edition” is a set of quantitative scoring system for drug evaluation and selection in Chinese medical institutions, which is widely used in China.

Evaluation of Drugs

Because of the existence of several different manufacturing units for calcitriol, alfacalcidol, and eldecacitol, drugs evaluated in this study are preferentially selected that have been listed in China and meet one of the following conditions: 1. Original research drug; 2. Included in the national centralized procurement list; 3. Included in the national essential drug list. It should be noted that all existed dosage forms were considered in the assessment and the researchers are medical institution workers independent from the product manufacturers.

The final drugs included in the evaluation are shown in Table 1.

Detailed Criteria for Quantitative Assessment of Drug Selection in Hospitals

A health technology assessment of the 8 OP drugs included in the study was performed according to “The Second Edition” and graded by a hundred mark system. The evaluation included five dimensions: Pharmaceutical properties,

Table 1 Drugs Included in the Evaluation

	Calcitriol			Alfacalcidol				Eldecacitol
	Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft capsules
Trade name	GAI SANCHUN	Rocaltrol	Calcijex	KANG CHEN	ONE-ALPHA	ONE-ALPHA	LI QING	EDIROL
Manufacturer	CP Pharmaceutical Qingdao Co. Ltd.	Roche Pharma (Schweiz) Ltd.	Abbvie Pte. Ltd.	Consun Pharmaceutical (Inner Mongolia) Co. Ltd	LEO Pharma Inc.	LEO Pharma Inc.	Yao Pharma (Chongqing) Co. Ltd.	Fujieda Plant of Chugai Pharma Manufacturing Co. Ltd
Specification	0.25µg*10 capsules/box	0.25µg*10 capsules/box	1mL:1µg/ vial	0.5µg*16 capsules/box	0.25µg*30 capsules/box	20mL:40µg/ bottle	0.25µg*30 tablets/ box	0.75µg*14 capsules/ box

efficacy, safety, economy, and other attributes. The specific index system and weighting coefficients were as follows: Pharmaceutical properties included pharmacological effects (5 points), in vivo processes (5 points), pharmacy and methods of use (12 points), storage conditions (4 points), and expiry date (2 points), totaling 28 points; efficacy included indications (5 points), guideline recommendations (12 points), and clinical efficacy (10 points), totaling 27 points; safety included adverse reactions (8 points), special populations (11 points), adverse reactions due to drug interactions (3 points), and others (3 points), totaling 25 points; economy included drugs with the same generic name (3 points) and alternative drugs for the main indications (7 points), totaling 10 points; and other attributes included the national health insurance (3 points), the national essential medicines (3 points), the national centralized purchasing of medicines (1 point), the original research drug / reference listed drug / consistency evaluation (1 point), the status of the manufacturing company (1 point), and the global use of the drug (1 point), totaling 10 points.

Quantitative Scoring Results and Recommendations

The scoring results have two primary uses according to “The Second Edition”: drug introduction and drug transfer, and the specific recommendations are detailed in [Table 2](#).

Results

Pharmaceutical Properties

The information was obtained from drug instructions, guidelines, Chinese and English databases, etc. The goal is to score the selected drugs on five aspects: pharmacological effects, in vivo processes, pharmacy and method of use, storage conditions, and expiry date.

Pharmacological Effects

The clinical efficacy and mechanism of action of the 8 drugs are apparent, and all of them scored 4 points;

In vivo Processes

The in vivo processes of the 8 drugs are clear, and the pharmacokinetic parameter is complete. All scored 5 points;

Pharmacy and Method of Use

The main components and excipients of alfacalcidol tablets are not identified, scored 1 point, and the other drugs are scored 2 points; in terms of specification and packaging, the 8 drugs are all suitable for clinical application or dose adjustment, all scored 2 points; in terms of dosage form, except for calcitriol injection, the other 7 drugs are oral dosage form, so calcitriol injection scored 1 point, and the other drugs scored 2 points; in terms of dosage administration, the 8 drugs need to formulate the optimal dosage according to the patient’s blood calcium level, all scored 1.5 points; in terms of the frequency of dosage administration, the recommended dosage for treating OP is twice daily for both calcitriol soft capsules I and II, scored 1.5 points. The recommended dose for calcitriol injection is three times weekly, every other day, scored 2 points. The rest of the drugs are once daily, scored 2 points; in terms of ease of use, except for calcitriol injection, which needs to be administered by medical personnel, scoring 1 point, the rest of the drugs can be self-administered, scored 2 points;

Table 2 Quantitative Scoring Results and Recommendation

Quantitative Rating	Recommendations for The Introduction of Drug	Recommendations for Drug Redeployment
>70 points	Recommended access to the Drug Utilization Catalog	Recommended for reserved use
70–60 points	Consider not to enter the Drug Utilization Catalog if alternative therapeutic drugs are available.	Consider transferring from the drug use list if alternative therapeutic drugs are available.
<60 points	Suggested not to enter the medical institution’s drug use catalog	Suggested to move out of the medical institution’s drug use catalog

Storage Conditions

Oral drops need to be refrigerated and protected from light, scored 1 point; alfacalcidol capsules, alfacalcidol soft capsules, eldecalcitol soft capsules need to be stored in the shade and protected from light, scored 2 points, while the other drugs need to be stored in room temperature and protected from light, scored 3 points.

Expiry Date

Calcitriol injection and alfacalcidol tablets only have 24 months, scored 1 point, while the other drugs have 36 months, scored 1.5 points.

The pharmaceutical properties score Results are shown in [Table 3](#).

Efficacy

Indications

The Indications of calcitriol, alfacalcidol, and eldecalcitol are all for the treatment of OP; the former two have been listed in the Chinese domestic market for many years, with rich experience in the clinical use of the drugs and more complete indications, while eldecalcitol was approved for the domestic market in 2022, and is currently only approved for the treatment of postmenopausal women with OP. Regarding indications, the eight drugs have more clinically available drugs, and all scored 1 point.

Guideline Recommendations

Checking the guideline query websites such as Yimaitong, Medication Assistant, Yaozhi Data, and Up to date database. Calcitriol and alfacalcidol were recommended in several guidelines. The highest recommendation grade for both was IA, and they both scored a guideline recommendation score of 12; Eldecalcitol did not have a high recommendation grade due to its late introduction to the Chinese market. It is recommended in the Guidelines for the Diagnosis and Treatment of Osteoporosis in Men,⁹ etc., so it scored 7 points; domestic and international guidelines or consensus recommendations are shown in [Table 4](#).

Clinical Efficacy

Check related drugs' RCT and meta-analysis literature to determine the clinical Efficacy.^{15–22} To determine the clinical efficacy, the degree of bone pain and itching of the patients after treatment was used as the primary efficacy endpoint indicators: reduction of the degree of pain and improvement of bone mineral density (BMD) after treatment was judged to be effective; no change or aggravation of the degree of pain, and no change or decrease in BMD was judged to be ineffective. In 2 studies,^{23,24} it was noted that in terms of BMD, eldecalcitol was more effective than alfacalcidol on BMD. A meta-analysis indicated that eldecalcitol was more effective than alfacalcidol in reducing bone turnover markers (BTM).²⁵ The primary efficacy endpoint indicator score was 6 for eldecalcitol and 5 for calcitriol and alfacalcidol. The degree of improvement in bone metabolism marker levels such as bone-specific alkaline phosphatase, blood calcium, and blood phosphorus after treatment was used as secondary efficacy endpoint indicators; the improvement in bone metabolism marker levels after treatment with eldecalcitol was more favorable²¹ so the score was 4 for eldecalcitol and 3 for both calcitriol and alfacalcidol.

The efficacy score results are shown in [Table 5](#).

Safety

The Safety assessment of the selected drugs was based on the drug instructions, drug registration information, information published on government websites such as the Food and Drug Administration (FDA) and the National Medical Protection Administration (NMPA), and relevant literature in both Chinese and English.^{26–30} The safety assessment of the drugs to be selected was based on the following four aspects: adverse drug reactions, use in special populations, drug interactions, and other aspects of safety.

Table 3 Pharmaceutical Properties Score Results

Pharmaceutical Properties (28 Points)		Grading Criteria	Calcitriol			Alfacalcidol				Eldecalcitol
			Soft capsules I	Soft capsules II	Injection	Capsules	Soft capsules	Oral drops	Tablets	Soft capsules
Pharmacological effects (5)	Definite clinical efficacy, precise mechanism of action, and innovative mechanism of action or target point of action	5								
	Definite clinical efficacy and precise mechanism of action	4	4	4	4	4	4	4	4	4
	Fair clinical efficacy and mechanism of action are unclear	2								
	General clinical efficacy and unclear mechanism of action	1								
In vivo processes (5)	Well-defined in vivo process with complete pharmacokinetic parameters	5	5	5	5	5	5	5	5	5
	Well-defined in vivo process with incomplete pharmacokinetic parameters	3								
	In vivo processes are unclear, or no pharmacokinetic studies are available	1								
Pharmacy and methods of use (multiple choice) (12)	Main ingredients and excipients (all specify 2; one specify 1)	2	2	2	2	2	2	2	1	2
	Specification and packaging (all appropriate for clinical use/dose adjustment 2; one appropriate 1)	2	2	2	2	2	2	2	2	2
	Dosage forms (oral/inhalation/topical formulations 2; subcutaneous/intramuscular injections 1.5; intravenous drip/intravenous injections 1)	2	2	2	1	2	2	2	2	2
	The dose administered (fixed dose 2; dose to be adjusted during use 1.5; dose based on body mass or body surface area 1)	2	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Frequency of administration (<1 dose/d 2; 2 doses/d 1.5; ≥3 doses/d 1)	2	1.5	1.5	2	2	2	2	2	2
	Ease of use (self-administration without assistance 2; with help or training 1.5; administered by medical personnel 1)	2	2	2	1	2	2	2	2	2
	Storage conditions (multiple choice)(4)									
	Expiry date (2)									
	Storage at room temperature	3	3	3	3			3		
	Storage in the shade	2				2	2			2
	Refrigerated/frozen storage	1						1		
	No need for shade/light protection	1								
	>60 months	2								
	≥36 months, <60 months	1.5	1.5	1.5		1.5	1.5	1.5		1.5
	≥24 months, <36 months	1			1				1	
	≥12 person-months, <24 months	0.5								
	<12 months	0.25								
Pharmaceutical Properties Score			24.5	24.5	22.5	24	24	23	23.5	24

Table 4 Recommendations from National and International Guidelines/Consensus

Name of the Guidelines	Guide Developers and Sources	Name of Drug	Recommended Content	Level of Evidence
Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology ¹⁰	The Italian Society for Orthopaedics and Traumatology (SIOT)	Calcitriol, Alfacalcidol	In subjects with CKD stages 4–5 and 5D with elevated parathyroid hormone, calcitriol and its analogs are able to reduce the levels of parathyroid hormone and favorably modify the alterations in bone metabolism (grade A recommendation).	I A
UK clinical guideline for the prevention and treatment of OP ¹¹	The UK National OP Guideline Group (NOGG)	Calcitriol	Calcitriol (1,25-dihydroxyvitamin D3) is the active form of vitamin D and is approved for the treatment of established postmenopausal osteoporosis in an oral dose of 0.25 µg twice daily.	II B
KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease- Mineral and Bone Disorder (CKD-MBD) ¹²	The USA National Kidney Foundation (NKF)	Calcitriol, Alfacalcidol	1. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B) 2. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 mL/min/1.73 m ² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D)	II B
Guidelines for the diagnosis and treatment of primary osteoporosis (2022) ¹³	Chinese Society of Osteoporosis and Bone Mineral Research	Calcitriol, Alfacalcidol, Eldecacitol	At present, the active vitamin D and its analogues listed in China for the treatment of osteoporosis are Alfacalcidol, Calcitriol and Eldecacitol. This type of drug is more suitable for the elderly, patients with reduced renal function, and 1 alpha-hydroxylase deficiency or reduction, and has been shown to increase bone density, reduce falls, and lower the risk of fractures.	/
Guidelines for the diagnosis and treatment of OP in men ⁹	Chinese Society of Osteoporosis and Bone Mineral Research	Calcitriol, Alfacalcidol, Eldecacitol	Anti-osteoporotic drugs in men with OP: calcitriol 0.25 µg, qd or bid, orally; alfacalcidol 0.25~1.0 µg/d, single or divided oral dose: eldecacitol (ED-71) 0.75 µg/d	/
Guideline for rational medication of osteoporosis in primary care ¹⁴	China Medical Association (CMA)	Calcitriol, Alfacalcidol	Alfacalcidol: adult 0.5µg/d, orally Calcitriol: 0.25µg/time, 2 times/d, orally	/

Notes: 2 guidelines^{10,12} were published when eldecacitol was not yet available in China, so calcitriol and its analogs which mentioned in the content included calcitriol and alfacalcidol (same as vitamin D analogs).

Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone.

Adverse Reactions

Refer to the CTCAE-V5.0 grading to determine the severity of adverse reactions of the drugs to be selected. Calcitriol, alfacalcidol, and eldecacitol, as active vitamin D, produce adverse reactions similar to those of vitamin D, mainly including hypercalcemia and hypercalciuria,³¹ and other adverse reactions include loss of appetite, headache, nausea, vomiting, abdominal pain, and constipation. However, post-marketing clinical use of calcitriol in soft capsules I and II showed a low incidence of adverse reactions (less than 0.001%). Post-marketing adverse reactions to calcitriol injection were mainly hypersensitivity (2.3%). Still, they were primarily mild pain and localized redness in the injected portion of

Table 5 Efficacy Score Results

Efficacy (27 Points)		Grading Criteria	Calcitriol			Alfacalcidol				Eldecalcitol
			Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft capsules
Indications (5)	Clinically necessary, preferred	5								
	Clinical need, second choice	3								
	More medicines available	1	1	1	1	1	1	1	1	1
Recommended Guidelines (12)	Diagnosis and treatment norms/clinical pathways, consensus issued by national health administrative agencies/management methods, etc., guideline level I recommendation (Level A evidence 12; Level B evidence 11; Level C evidence, and others 10)	12	12	12	12	12	12	12	12	
	Guidelines Level II and below (Level A Evidence 9; Level B Evidence 8; Level C Evidence and Others 7)	9								7
	Expert Consensus Recommendations (the consensus published by the society organizations based on systematic evaluation 6; the consensus published by the society organization others 4)	6								
	Systematic evaluation/Meta-analysis (large sample, high-quality systematic evaluation/Meta-analysis 3; small sample, low-quality systematic evaluation/Meta-analysis 2; systematic evaluation/Meta-analysis of non-RCT studies 1).	3								
Clinical efficacy (10)	The primary efficacy endpoint indicators (6)	6	5	5	5	5	5	5	5	6
	The secondary efficacy endpoint indicators (4)	4	3	3	3	3	3	3	3	4
Efficacy Score			21	21	21	21	21	21	21	18

the injection and were not considered moderate adverse reactions. Therefore, this item scored 8 points. Alfacalcidol soft capsules and oral drops are both products of Leo Pharmaceuticals (Denmark) Ltd. In the bioavailability study conducted by the company, it was suggested that the adverse reactions were mainly caused by overdose, and the related symptoms were mostly mild adverse reactions such as itching, headache, nausea, excessive thirst, constipation, etc. Therefore, both of them scored 8 points in this item. Alfacalcidol tablets and alfacalcidol capsules in treating OP adverse reactions are mainly loss of appetite, vomiting, and other mild adverse reactions, so both scored 8 points. Eldecalcitol as a new type of active vitamin D, post-marketing adverse reaction data are limited, but in the clinical trials conducted in Japan, in addition to the frequency of acute renal failure is not known, the incidence of hypercalcemia and urinary stones was 1.5%, 0.9%. Therefore, 2 points were awarded for "severe adverse reactions", and the total score for this item was 5 points.

Special Populations

(1) Children: The safety of calcitriol and eldecalcitol in children has not been adequately studied, and there is no reliable literature, so both have no point in this item. Alfacalcidol soft capsules and oral drops instructions for children with different body weights to use the dose precise instructions, so both scored 2 points in this item. The rest of the drugs did not score. (2) Elderly: Elderly patients do not need particular dosages for calcitriol soft capsules I and soft capsules II, so this item scored 1 point. When using calcitriol injection, the dosage selection for elderly patients should be cautiously treated, so this item scores 0.5 points. Caution should be exercised when elderly patients use alfacalcidol tablets and eldecalcitol soft capsules, so both score 0.5 points. The rest of the drugs do not have specific use experience in the elderly, and no point should be scored. (3) Pregnant women: There are no appropriate and well-controlled trials to study the effects of calcitriol on pregnant women. Therefore, all forms of calcitriol are not scored. Based on the package insert, alfacalcidol should be used with caution in pregnant women. To differentiate from situations such as prohibition or absence of relevant studies, alfacalcidol in all dosage forms scored 0.5 points for this. Eldecalcitol is contraindicated in pregnant women, so eldecalcitol soft capsules are not scored. (4) Lactating women: Domestic instructions for calcitriol capsules II state that mothers can breastfeed while taking the product if they monitor calcium levels in both the mother and the baby. Therefore, the calcitriol soft capsules II will receive 0.5 points for this item, and no points will be awarded for the remaining dosage forms of calcitriol. If the risks have been weighing, alfacalcidol soft capsules, oral drops, and capsules should only be used on medical advice. Therefore, scored 0.5 points. Alfacalcidol tablets should preferably be avoided during breastfeeding but are not strictly prohibited, so this item scored 0.5 points. The use of eldecalcitol soft capsules is prohibited during lactation, so are not scored. (5) Hepatic dysfunction: Only the eldecalcitol soft capsules have been studied on the pharmacokinetics of patients with hepatic dysfunction, suggesting that the safety of patients with severe hepatic dysfunction has not been established and should be cautiously administered. Therefore, the eldecalcitol soft capsules scored 2 points, and the rest of the drugs scored 0 points. (6) Renal dysfunction: refer to the Consensus³² on the Clinical Use of Vitamin D and its Analogs. Calcitriol and its analogs may be considered in CKD patients with combined OP and/or high fracture risk. Therefore, all drugs included in the study scored 3 points for this item.

Drug Interactions

Calcitriol, alfacalcidol, and eldecalcitol are active vitamin D. Therefore, pharmacologic doses of vitamin D and its derivatives should be suspended when taking them. Its combination with magnesium-containing drugs (such as antacids) may cause an increase in the concentration of magnesium ions in the blood, which can lead to hypermagnesemia, so long-term dialysis patients are prohibited from taking it at the same time. In addition, when taking active vitamin D, thiazides and digitalis should be avoided as much as possible, so all drugs included in the study received a score of 1 for this item.

Other Aspects of Safety

All adverse reactions of the drugs included in the study were reversible and scored 1 point. No carcinogenicity was seen with all the drugs included in the study. Calcitriol soft capsules I and II showed no adverse effects on reproductive toxicity studies. The rest suggest that high doses may cause fetal malformations, so calcitriol soft capsules I and II scored 1 point, and the rest did not score any points. The instructions for all drugs have no special medication warning, and all scored 1 point. In conclusion, calcitriol soft capsules I and II scored 3 points, and the rest scored 2 points.

The safety score results are shown in [Table 6](#).

Table 6 Safety Score Results

Safety (25 Points)		Grading Criteria	Calcitriol			Alfacalcidol				Eldecalcitol
			Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft Capsules
Moderate adverse reactions (3)	Incidence <1%	3	3	3	3	3	3	3	3	3
	Incidence 1% to <10%	2								
	Incidence ≥10%	1								
Severe adverse reactions (5)	ADR occurrence data not available	0								
	Incidence < 0.01%	5	5	5	5	5	5	5		
	Incidence 0.01%~<0.1%	4								
	Incidence 0.1%~<1%	3								
	Incidence 1% to <10%	2								2
Special populations (multiple choice) (11)	Incidence ≥10%	1								
	ADR occurrence data not available	0								
	Available for children (both 2; 1.9 for 3 months+; 1.8 for 6 months+; 1.7 for 9 months+; 1.6 for ages 1+; 1.5 for ages 2+; 1.4 for ages 3+; 1.3 for ages 4+; 1.2 for ages 5+; 1.1 for ages 6+; 1.0 for ages 7+; 0.9 for ages 8+; 0.8 for ages 9+ 0.7 for ages 10+; 0.6 for ages 11+; 0.5 for ages 12+.	2	0	0	0	0	2	2	0	0
	The elderly (available 1; use with caution 0.5)	1	1	1	0.5	0	0	0	0.5	0.5
	Pregnant women (early pregnancy 1; during the first trimester 0.8; during the second trimester 0.5).	1	0	0	0	0.5	0.5	0.5	0.5	0
	Lactating women (available 1; use with caution 0.5)	1	0	0.5	0	0.5	0.5	0.5	0.5	0
	Hepatic dysfunction (severe available 3, moderate available 2.	3	0	0	0	0	0	0	0	2
	Lightly available 1)									
	Renal dysfunction (severe available 3, moderate available 2.	3	3	3	3	3	3	3	3	3
	Lightly available 1)									
	Adverse reactions due to drug interactions (3)	No dosage adjustment is required	3							
Dosage adjustment required		2								
Prohibited to use at the same time		1	1	1	1	1	1	1	1	1
Other (multiple choice) (3)	Reversibility of adverse reactions	1	1	1	1	1	1	1	1	1
	Non-teratogenic/ non-carcinogenic	1	1	1	0	0	0	0	0	0
	No special medication warnings	1	1	1	1	1	1	1	1	1
Safety Score			16	16.5	14.5	15	17	17	15.5	13.5

Economy

The economic study was conducted by comparing the difference in average daily treatment costs between the selected drugs and those with the same generic name and substitutable drugs for the main indications. The information was obtained from drug pricing information released by the Yaozhi Data, the National Centralized Purchasing Platform for Drugs, the Sunshine Purchasing Platform, information on corporate websites, NMPA, the National Medical Protection Administration, and other information on governmental websites. All information counted as of July 1, 2023.

Drugs with the Same Generic Name

The lowest average daily cost of treatment for the same generic name is 3 points, and the evaluation drug score = the lowest average daily cost of treatment / average daily cost of treatment for the evaluated drug * 3. Calcitriol injection, alfacalcidol capsules, and alfacalcidol oral drops are currently listed in the domestic market by only one manufacturer; all scored 3 points: Calcitriol soft capsules II (In China, its generic name is different from other calcitriol soft capsules), alfacalcidol tablets have the lowest average daily cost of treatment among the same generic name, all scored 3 points; calcitriol soft capsules (Sichuan Guowei Pharmaceutical Co. Ltd), with an average daily cost of 0.63 yuan, according to the evaluation method, calcitriol soft capsules I score of 1.82 points. The price of the cheapest alfacalcidol soft capsules (CP Pharmaceutical Qingdao Co. Ltd). is 3.76 yuan, so the evaluated alfacalcidol soft capsules score of 2.64 points; eldecacitol soft capsules (Wenzhou Haihe Pharmaceutical Co., Ltd). is the cheapest daily treatment option with the same generic name, priced at 3.6 yuan. According to the evaluation method, the eldecacitol soft capsule score is 2.95 points. See [Tables 7](#) and [8](#) for details.

Substitutable Medicines for Main Indications

The drug with the lowest average daily treatment cost of the same kind of drug is scored 7 points, and the evaluation drug score = the lowest average daily treatment cost/the average daily treatment cost of the evaluated drug * 7. Among the leading drugs for OP, the drug with the lowest average daily treatment cost is calcitriol soft capsules (Sichuan Guowei Pharmaceutical Co. Ltd), with an average daily cost of 0.63 yuan; the corresponding scores were calculated according to the evaluation method, and the score of the calcitriol soft capsules I, calcitriol soft capsules II, calcitriol injection, alfacalcidol capsules, alfacalcidol soft capsules, alfacalcidol oral drops, alfacalcidol tablets, and eldecacitol soft capsules were scored as 4.24, 0.52, 0.60, 1.62, 1.03, 0.36, 1.79, and 1.20 respectively. See [Tables 7](#) and [8](#) for details.

Other Attributes

Relevant information from National Essential Drug List (2018 Edition), National Medical Insurance List (2023 Edition), National Centralized Purchasing Drug List; drug packaging/instructions, China List of Listed Drugs Collection, NMPA Center For Drug Evaluation, FDA, European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) ; status of manufacturers from world sales of the top 50 pharmaceutical manufacturers published by US Pharmaceutical Managers, and the list of the top 100 pharmaceutical industry published by Ministry of Industry and Information Technology (MIIT).

Calcitriol injection and eldecacitol soft capsules are in National Medical Insurance Category B with payment restrictions, which scored 1.5 points, other evaluated drugs are in National Medical Insurance Category B without payment restrictions, scored 2 points. All dosage forms of calcitriol and eldecacitol soft capsules are not in the National Essential Drugs Catalog (2018 Edition), and all of them scored 1 point; all dosage forms of alfacalcidol belong to the National Essential Drugs, of which oral drops have Δ requirements, scored 2 points, and other dosage forms scored 3 points. Calcitriol soft capsules I, alfacalcidol soft capsules, and alfacalcidol tablets are in the National Centralized Purchasing Drug Catalogue, which scored 1 point, and the other drugs are not, which scored no points. Calcitriol soft capsules II, alfacalcidol soft capsules, and eldecacitol soft capsules all belong to the original research drug, and scored 1 point; calcitriol soft capsules I and alfacalcidol tablets passed the consistency evaluation, all scored 0.5 points, the others do not score. Calcitriol capsules II belong to Roche Group, calcitriol injection belongs to AbbVie Group, and both belong to the world's top 10 pharmaceutical manufacturers in terms of sales in 2022, scored 1 point. Eldecacitol soft capsules belong to Chugai Group, which is in the 35th position of the world sales ranking in 2022 scored 0.4 points. The manufacturers of Calcitriol soft capsules I and all dosage forms of alfacalcidol are not in the 2022 World Sales Top 50/ MIIT 's Top 100 Pharmaceutical Industry list, and all are not scored. Calcitriol soft capsules I, alfacalcidol

Table 7 Basic Economy Information

	Calcitriol			Alfacalcidol				Eldecalcitol
	Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft Capsule
Specification	0.25 μ g*10	0.25 μ g*10	1mL:1 μ g	0.5 μ g*16	0.25 μ g*30	10mL/vial (2 μ g/mL)	0.25 μ g*30	0.75 μ g*14
Dosage	2 times/d, 1 capsule/time	2 times/d, 1 capsule/time	0.5mL/dose, 3 times/week, every other day	1 time/d, 1 capsule/time	1 time/d, 4 capsules/time	0.5mL/d	1 time/d, 2 tablets/time	1 time/d, 1 capsule/time
Average daily cost of treatment (¥)	1.04	8.47	7.33	2.73	4.27	12.1	2.46	3.66
Drug scores with the same generic name	1.82	3.00	3.00	3.00	2.64	3.00	3.00	2.95
Substitutable Drug Score for Primary Indications	4.24	0.52	0.60	1.62	1.03	0.36	1.79	1.20

Table 8 Economy Score Results

Economy (10 Points)		Grading Criteria	Calcitriol			Alfacalcidol				Eldecalcitol
			Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft Capsules
Drugs with the same generic name (3)	The score for the evaluated drug = lowest average daily cost of treatment/average daily cost of treatment for the evaluated drug * 3	3	1.82	3	3	3	2.64	3	3	2.95
Substitutable medicines for main indications (7)	The score for the evaluated drug = lowest average daily cost of treatment / average daily cost of treatment of the evaluated drug * 7.	7	4.24	0.52	0.6	1.62	1.03	0.36	1.79	1.2
Economy Score			6.06	3.52	3.6	4.62	3.67	3.36	4.79	4.15

capsules and alfacalcidol tablets are only listed and sold within China, with no score. Calcitriol soft capsules II listed in all of the United States, Europe, and Japan, scored 1 point. and others are sold domestically and internationally but are not listed in all of the United States, Europe, and Japan scored 0.5 points.

The other attribute score results are shown in [Table 9](#).

Discussion

Significance of the Assessment

Currently, there are no unified standards for the admission and transfer of medicines to and from medical institutions in China. To establish a sound drug supply security system, “The Second Edition” improved drug evaluation in medical institutions for better prioritization and compliance with national policy. And at the same time, the scoring entries are more detailed, clearer, and easier to operate.

Active vitamin D is a commonly used preventive and curative drug for OP. This study provides a rapid health assessment of 2 clinically typical active vitamin Ds (calcitriol, alfacalcidol) and a new active vitamin D (eldecalcitol) for each dosage form through “The Second Edition”, guide medical institutions in selecting drugs that align with patient needs.

Description of the Assessment and Analysis of Results

The drugs included in this study in descending order of quantitative final scores were alfacalcidol soft capsules, calcitriol soft capsules I, calcitriol soft capsules II, alfacalcidol tablets, alfacalcidol capsules, alfacalcidol oral drops, calcitriol injection, eldecalcitol soft capsules. The final total scores shown in [Table 10](#), were 73.17, 72.06, 71.52, 71.29, 69.62, 68.86, 65.6, and 64.05 points respectively.

In the final score, the top four drugs with the highest scores were alfacalcidol soft capsules, calcitriol soft capsules I, calcitriol soft capsules II, alfacalcidol tablets. All are recommended for treating OP, with scores over 70. Among them, calcitriol soft capsules I have a more significant economic advantage compared with the other 7 drugs; alfacalcidol soft capsules, alfacalcidol tablets are national essential drugs, and in the national centralized purchasing in the selection, have a more significant policy advantage; calcitriol soft capsules II are a well-established drug with positive clinical experience and recommended for treating OP.

The scores of other drugs (calcitriol injection, alfacalcidol capsules, alfacalcidol oral drops, and eldecalcitol soft capsules) are located between 60 and 70, which are weakly recommended, and medical institutions can choose according to the actual situation. It is worth mentioning that the lowest-scoring eldecalcitol soft capsule, as a new type of active vitamin D, has been on the market for a shorter period in China, with limited clinical data, and is less often recommended by the guidelines. However, its effectiveness is better than the other 7 drugs, and it is the only drug in this study that has been studied in the population with hepatic insufficiency.

Shortcomings and Limitations

“The Second Edition” has been refined based on the former, but in the actual evaluation, we found that some of the scoring rules are still imperfect. For example, when evaluating pharmaceutical properties, the main ingredient and excipients have the same weight, but in practice, they should be distinguished in the light of their clinical importance.

In the process of evaluation, subjectivity is inevitable. For example, in the assessment of the efficacy of drugs, there are many primary and secondary efficacy endpoints in the literature, and they are not uniform; in the evaluation of the safety of drugs, it is hard to accurately categorize them into any of the available cases because the instructions or some of the literature do not indicate the stage of pregnancy in which pregnant women in special populations can use the drug, or only indicate that it should be used with caution.

The final score derived from this selection guideline is time-sensitive. As evidence-based evidence such as guidelines, expert consensus, and adverse reaction reports are updated, the final score based on the selection guidelines may change. Due to the differences in policies and hospital management models in different regions, it is necessary to keep an eye on this information when applying it in clinical practice, discuss the actual situation of each medical institution in each region, and reevaluate the drugs when necessary.

Table 9 Other Attribute Score Results

Other attributes (10 Points)		Grading Criteria	Calcitriol			Alfacalcidol				Eldecalcitol
			Soft Capsules I	Soft Capsules II	Injection	Capsules	Soft Capsules	Oral Drops	Tablets	Soft Capsules
National medical insurance (3)	National medical insurance category A, no payment restrictions	3								
	National medical insurance category A with payment restrictions	2.5								
	National medical insurance category B, no payment limitations	2	2	2		2	2	2	2	
	National medical insurance category B with payment restrictions.	1.5			1.5					1.5
National essential drugs (3)	Not on the national medical insurance list	1								
	National essential drugs without Δ requirement.	3				3	3		3	
	National essential drugs with Δ Requirements	2						2		
National centralized procurement of medicines (1)	Not on the national essential drugs list	1	1	1	1					1
	Selected drugs for centralized national procurement	1	1				1		1	
Original/reference/consistency evaluation (1)	Drug of origin/reference drug	1		1			1			1
	Generic drugs through consistency evaluation	0.5	0.5						0.5	
Status of manufacturers (1)	The world's top 50 pharmaceutical manufacturers in terms of sales volume (1 for top1-10; 0.8 for top11-20; 0.6 for top21-30; 0.4 for top31-40; 0.2 for top41-50) / Top 100 Pharmaceutical Industry published by MIIT (1 for top1-20; 0.8 for top21-40; 0.6 for top41-60; 0.4 for top61-80; 0.2 for top81-100).	1		1	1					0.4
Global utilization (1)	Available in China, USA, Europe, Japan	1		1						
	Domestic and international sales	0.5			0.5		0.5	0.5		0.5
Other Attributes Score			4.5	6	4	5	7.5	4.5	6.5	4.4

Notes: The “ Δ ” sign indicates that the drug should be used by a physician with corresponding prescription qualifications or under the guidance of a specialist physician, and use monitoring and evaluation should be strengthened.

Table 10 Final Total Score Results

Evaluation Dimension	Calcitriol Soft Capsules I	Calcitriol Soft Capsules II	Calcitriol Injection	Alfacalcidol capSules	Alfacalcidol Soft Capsules	Alfacalcidol Oral Drops	Alfacalcidol Tablets	Eldecalcitol Soft Capsules
Pharmaceutical Properties	24.5	24.5	22.5	24	24	23	23.5	24
Efficacy	21	21	21	21	21	21	21	18
Safety	16	16.5	14.5	15	17	17	15.5	13.5
Economy	6.06	3.52	3.6	4.62	3.67	3.36	4.79	4.15
Other Attributes	4.5	6	4	5	7.5	4.5	6.5	4.4
Total Score	72.06	71.52	65.6	69.62	73.17	68.86	71.29	64.05

Conclusion

Alfacalcidol soft capsules, calcitriol soft capsules I, calcitriol soft capsules II, alfacalcidol tablets can be entered into the medication list of medical institutions as strongly recommended drugs. This health technology assessment can provide evidence-based evidence for the selection and rational use of active vitamin D, and also serve as a reference for hospitals in other countries to select drugs.

Acknowledgments

We would like to thank all of the authors that participated in the present study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Key Specialty Construction Project (Clinical Pharmacy) and the High-level Clinical Key Specialty of Guangdong Province, and the funders were the central finance subsidy fund for the improvement of medical services and guarantee capacity, code Z155080000004; the Guangzhou Minsheng Science and Technology Research Program Project, code 201803010096.

Disclosure

The authors report no conflicts of interest in this work.

References

1. WA P. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94(6):646–650. doi:10.1016/0002-9343(93)90218-e
2. Zhang H, Hu Y, Chen X, et al. Expert consensus on the bone repair strategy for osteoporotic fractures in China. *Front Endocrinol.* 2022;13:989648. doi:10.3389/fendo.2022.989648
3. Xi X, Mehmood A, Niu P, et al. Association of X-linked TLR-7 gene polymorphism with the risk of knee osteoarthritis: a case-control study. *Sci Rep.* 2022;12(1):7243. doi:10.1038/s41598-022-11296-4
4. Bischoff-Ferrari HA, Dawson-Hughes B, Stachelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomized controlled trials. *BMJ.* 2009;339:b3692. doi:10.1136/bmj.b3692
5. de Freitas PH, Hasegawa T, Takeda S, et al. Eldecalcitol, a second-generation vitamin D analog, drives bone mini modeling and reduces osteoclastic number in trabecular bone of ovariectomized rats. *Bone.* 2011;49(3):335–342. doi:10.1016/j.bone.2011.05.022
6. Matsumoto T, Takano T, Saito H, Takahashi F. Vitamin D analogs and bone: preclinical and clinical studies with eldecalcitol. *Bonekey Rep.* 2014;3:513. doi:10.1038/bonekey.2014.8
7. Matsumoto T, Ito M, Hayashi Y, et al. A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures--a randomized, active comparator, double-blind study. *Bone.* 2011;49(4):605–612. doi:10.1016/j.bone.2011.07.011
8. Zhao Z, Dong Z, Liu J. A quick guideline for drug evaluation and selection in Chinese medical institutions(the Second Edition). *Herald Med.* 2023; (04):447–456. doi:10.3870/j.issn.1004-0781.2023.04.001

9. Chinese Society of Osteoporosis and Bone Mineral Research. Guidelines for the diagnosis and treatment of osteoporosis in men. *Chin J Osteop Bone Min Res.* 2020;5:381–395. doi:10.3969/j.issn.1674-2591.2020.05.001
10. Tarantino U, Iolascon G, Cianferotti L, et al. Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol.* 2017;18(Suppl 1):3–36. doi:10.1007/s10195-017-0474-7
11. Compston J, Cooper A, Cooper C, et al.; National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteop.* 2017;12(1):43. doi:10.1007/s11657-017-0324-5
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7(1):1–59. doi:10.1016/j.kisu.2017.04.001
13. Chinese Society of Osteoporosis and Bone Mineral Research. Guidelines for the diagnosis and treatment of primary osteoporosis(2022). *Chin J Osteop Bone Min Res.* 2022;06:573–611. doi:10.3969/j.issn.1674-2591.2022.06.001
14. Chinese Medical Association, Chinese Society of Clinical Pharmacy, Chinese Medical Journals Publishing House, et al. Guideline for rational medication of osteoporosis in primary care. *Chin J Gen Practit.* 2021;5:523–529. doi:10.3760/cma.j.cn114798-20210318-00258
15. Zhao J, Mou A, Mao J, Zhu X. Clinical efficacy of different doses of intravenous calcitriol in the treatment of secondary hyperparathyroidism for hemodialysis patients. *Chin J Coal Ind Med.* 2018;1:53–57.
16. Gui G, Han Z, Xu Y, Wang F, Xia X. Clinical efficacy of calcitriol injection and oral shock therapy in patients with secondary hyperparathyroidism. *West Med.* 2019;2:282–286+290.
17. Pang XP. Clinical efficacy of calcitriol combined with Telmisartan in the treatment of diabetic nephropathy. *Chin Mod Doctor.* 2013;20:52–54.
18. Liu LH. Clinical effect of calcitriol on 40 cases of uremia complicated with renal bone disease. *Mod Diagn Treat.* 2014;09:1983–1984.
19. Tang H, Wang Z. Effect of Alfacalcidol soft capsules combined with bone peptide injection on osteoporosis. *Med Theor Pract.* 2019;19:3113–3115. doi:10.19381/j.issn.1001-7585.2019.19.037
20. Shen L, Liu P, Zhu S. Alfacalcidol soft capsules combined with raloxifene in the treatment of postmenopausal osteoporosis. *Modern Med Clin.* 2017;(07):1328–1332. doi:10.7501/j.issn.1674-5515.2017.07.038
21. Cui L, Xia W, Yu C, Dong S, Pei Y. Overview of the clinical efficacy and safety of eldelcalcitol for the treatment of osteoporosis. *Arch Osteop.* 2022;17(1):74. doi:10.1007/s11657-022-01071-3
22. Lin Q, Tan R. Meta-analysis of the effects of calcitriol on microinflammation and calcium and phosphorus metabolism in maintenance hemodialysis patients. *Chin Contemp Med.* 2022;36:13–17. doi:10.3969/j.issn.1674-4721.2022.36.005
23. Liu H, Wang G, Wu T, Mu Y, Gu W. Efficacy and safety of eldelcalcitol for osteoporosis: a meta-analysis of randomized controlled trials. *Front Endocrinol.* 2022;13:854439. doi:10.3389/fendo.2022.854439
24. Nakamura T, Takano T, Fukunaga M, Shiraki M, Matsumoto T. Eldelcalcitol is more effective for the prevention of osteoporotic fractures than alfacalcidol. *J Bone Miner Metab.* 2013;31(4):417–422. doi:10.1007/s00774-012-0418-5
25. Xu Z, Fan C, Zhao X, Tao H. Treatment of osteoporosis with eldelcalcitol, a new vitamin D analog: a comprehensive review and meta-analysis of randomized clinical trials. *Drug Des Devel Ther.* 2016;10:509–517. doi:10.2147/DDDT.S84264
26. Jiang Y, Xing P, Li M, Wang O, Xia W. Efficacy and safety of alfacalcidol in osteoporosis: a meta-analysis. *Chin J Osteop Bone Min Res.* 2021;03:221–229. doi:10.3969/j.issn.1674-2591.2021.03.001
27. Takeuchi Y, Saito H, Makishima M, et al. Long-term safety of eldelcalcitol in Japanese patients with osteoporosis: a retrospective, large-scale database study. *J Bone Miner Metab.* 2022;40(2):275–291. doi:10.1007/s00774-021-01276-5
28. Kawahara T, Suzuki G, Mizuno S, et al. Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population. *BMJ.* 2022;377:e066222. doi:10.1136/bmj-2021-066222
29. Laskou F, Fuggle NR, Patel HP, Jameson K, Cooper C, Dennison E. Associations of osteoporosis and sarcopenia with frailty and multimorbidity among participants of the Hertfordshire cohort study. *J Cach Sarcop Mus.* 2022;13(1):220–229. doi:10.1002/jcsm.12870
30. Maeda K, Imatani J, Moritani S, Kondo H. Effects of eldelcalcitol alone or a bone resorption inhibitor with eldelcalcitol on bone mineral density, muscle mass, and exercise capacity for postmenopausal women with distal radius fractures. *J Orthop Sci.* 2022;27(1):139–145. doi:10.1016/j.jos.2020.11.009
31. Ringe JD. Plain vitamin D or active vitamin D in the treatment of osteoporosis: where do we stand today? *Arch Osteop.* 2020;15(1):182. doi:10.1007/s11657-020-00842-0
32. Xia W, Zhang Z, Lin H, Jin X, Yu W, Fu Q. the consensus on the clinical use of vitamin D and its analogs. *Chin J Osteop Bone Min Res.* 2018;01:1–19. doi:10.3969/j.issn.1674-2591.2018.01.001

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>