

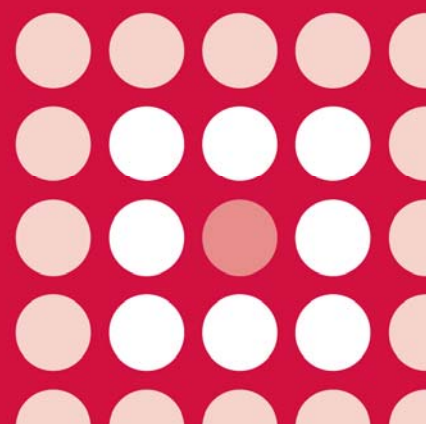


All Wales Therapeutics  
and Toxicology Centre  
Canolfan Therapiwteg a  
Thocsicoleg Cymru Gyfan

**AWMSG SECRETARIAT ASSESSMENT REPORT  
(FULL SUBMISSION)**

# Advice No. 3612

**Colecalciferol (Fultium-D<sub>3</sub><sup>®</sup>) 800 IU capsules**



## AWMSG Secretariat Assessment Report – Advice No. 3612 Colecalciferol (Fultium-D<sub>3</sub><sup>®</sup>) 800 IU capsules

This assessment report is based on evidence submitted by Internis Pharmaceuticals Ltd on 24 May 2012<sup>1</sup>.

### 1.0 PRODUCT DETAILS

<b>Licensed indication under consideration</b>	<p>Colecalciferol (Fultium-D<sub>3</sub><sup>®</sup>) is licensed:</p> <ul style="list-style-type: none"> <li>• For the prevention and treatment of vitamin D deficiency.</li> <li>• As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.</li> </ul> <p>Fultium-D<sub>3</sub><sup>®</sup> is indicated in adults, the elderly and adolescents<sup>2</sup>.</p>
<b>Dosing</b>	<p>Vitamin D deficiency in adults and the elderly (serum levels &lt; 25 nanomol/l [<math>&lt; 10</math> nanograms/ml]): 1–4 capsules (800–3,200 IU) daily for up to 12 weeks dependent upon the severity of the disease and the patient's response to treatment.</p> <p>Vitamin D insufficiency in adults and the elderly (serum levels 25–50 nanomol/l [10-20 nanograms/ml]), long-term maintenance therapy following treatment of deficiency in adults and the elderly, and prevention of vitamin D deficiency: 1–2 capsules (800–1,600 IU) daily.</p> <p>Vitamin D deficiency or insufficiency in children over 12 years: one capsule daily depending on the severity of the disease and the patient's response to treatment. Should only be given under medical supervision.</p> <p>As an adjunct to specific therapy for osteoporosis: one capsule daily<sup>2</sup>.</p>
<b>Marketing authorisation date</b>	28 October 2011 <sup>3</sup>

### 2.0 DECISION CONTEXT

#### 2.1 Background

Vitamin D is an essential hormone in calcium homeostasis. Vitamin D<sub>3</sub> is synthesised within the human body by the action of ultraviolet B sunlight on 7-dehydrocholesterol, before ultimately being converted to 1,25-dihydroxyvitamin D<sub>3</sub>. Plant vitamin D (D<sub>2</sub>) from the diet is also metabolised by dihydroxylation after absorption from the gut<sup>4</sup>; however, sun exposure is the most important vitamin D source<sup>3</sup>.

Vitamin D levels are measured using 25-hydroxyvitamin D<sub>3</sub> (25(OH)D) concentration<sup>3</sup>. Levels below 25 nanomol/l indicate a deficiency state with the risk of developing rickets or osteomalacia due to malabsorption of calcium and phosphorous<sup>3</sup>, which lead to undermineralisation of bone with accompanying weakness, tenderness and bone pain<sup>3</sup>.

The National Institute for Health and Clinical Excellence (NICE) have issued guidance on the treatment options for primary prevention of fragility fractures in postmenopausal

women with osteoporosis. This guidance recommends that patients should be considered for calcium and/or vitamin D supplementation unless clinicians are confident that the patient has adequate calcium intake and are vitamin D replete<sup>5</sup>.

Clinical guidelines recommend monotherapy for the treatment of vitamin D deficiency and suggest that colecalciferol is the preferred form of vitamin D for replacement therapy<sup>3,6-10</sup>. Fultium-D<sub>3</sub><sup>®</sup> (20 micrograms [800 IU]/day) is the only colecalciferol monotherapy licensed in the UK for the prevention and treatment of vitamin D deficiency. It should be noted that the dose of Fultium-D<sub>3</sub><sup>®</sup> is higher than that recommended by the UK Chief Medical Officers in their advice for supplements in at-risk groups<sup>11</sup>.

## 2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were ergocalciferol and unlicensed colecalciferol.

## 2.3 Guidance and related advice

The following national guidelines are available:

- Department of Health. Vitamin D – advice on supplements for at risk groups (2012)<sup>11</sup>.
- NICE Technology Assessment 160. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended) (2011)<sup>5</sup>.
- NICE Clinical Guideline 62. Antenatal care: Routine care for the healthy pregnant woman (2008)<sup>12</sup>.
- NICE Clinical Guideline 32. Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition (2006)<sup>13</sup>.

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes a literature-based assessment of the efficacy of vitamin D supplementation<sup>1</sup>; it summarises four meta-analyses<sup>14-17</sup> and a number of supporting studies<sup>18-22</sup>; however no studies specifically use Fultium-D<sub>3</sub><sup>®</sup>. Only the studies most relevant to the licensed indication will be included in this section. The Medicines and Healthcare products Regulatory Agency (MHRA) were satisfied that no new clinical or non-clinical efficacy studies were required to support the application for a licence, as the therapeutic use and safety profile of colecalciferol is well established.

### 3.1 Summary of supporting studies

Two small randomised controlled trials demonstrated that administration of colecalciferol (1,000 or 2,000 IU/day) to vitamin D-deficient patients led to an increase in 25(OH)D levels at six months, compared to baseline<sup>18</sup> and placebo<sup>19</sup>. A randomised trial (n = 64) that compared ergocalciferol and colecalciferol (dosed either daily [1,600 IU] or monthly [50,000 IU]) demonstrated that at one year, supplementation with colecalciferol was significantly more effective in raising 25(OH)D concentrations than ergocalciferol (13%; 95% confidence interval [CI]: 3–23%; p = 0.01)<sup>20</sup>. The company submission also included an 18-month study examining the effect of supplementation with both vitamin D<sub>3</sub> (800 IU/day) and calcium (1,200 mg/day) versus placebo in 3,270 healthy, ambulatory elderly women; this showed a 43% reduction in the incidence of hip fractures (p = 0.043) and a 32% reduction in other nonvertebral fractures (p = 0.015) in the supplemented group compared to placebo<sup>21</sup>.

### 3.2 Summary of meta-analyses

A meta-analysis of the effect of vitamin D on bone density and incidence of fractures in post-menopausal women identified 25 trials (n = 8,124)<sup>17</sup>. Vitamin D was found to reduce the incidence of vertebral fractures compared to the control group (relative risk [RR] of 0.63; 95% CI: 0.45–0.88, p < 0.01). There was also a trend towards reduction in nonvertebral fractures (RR 0.77; 95% CI: 0.57–1.04, p < 0.09). Discontinuing treatment with vitamin D due to adverse events or abnormal laboratory results revealed an increase in risk of morbidity compared to the control group (RR 1.37; 95% CI: 1.01–1.88, p = 0.05)<sup>17</sup>.

A meta-analysis conducted by Bischoff-Ferrari and colleagues examined the efficacy of various doses of oral vitamin D in preventing nonvertebral and hip fractures in elderly patients (≥ 65 years)<sup>15</sup>. This included 20 randomised controlled trials (n = 83,165) comparing oral vitamin D, with or without calcium, with calcium alone or placebo. For all trials, the anti-fracture efficacy increased significantly with higher doses of vitamin D (> 400 IU/day) and higher concentrations of 25(OH)D. Some of the heterogeneity of the data was removed by pooling data from trials where the vitamin D supplementation was > 400 IU/day. The pooled RR for nonvertebral fractures was 0.80; 95% CI: 0.72–0.89, n = 33,265; and for hip fractures was 0.82; 95% CI: 0.69–0.97, n = 31,872<sup>15</sup>.

A meta-analysis published in July 2012 was identified by AWTTTC and showed that a subgroup analysis of persons 65 years of age or older that received 792–2,000 IU/day vitamin D supplementation alone or in combination with calcium (n = 3,966) had a 30% reduction in the risk of hip fracture (p < 0.001), and a 14% reduction in the risk of nonvertebral fracture (p = 0.007) when compared with control (placebo or calcium alone)<sup>23</sup>.

### 3.3 Comparative safety

Although there are no comparative safety studies for Fultium-D<sub>3</sub><sup>®</sup>, the UK Public Assessment Report (PAR) prepared by the MHRA states that there are no new safety issues or concerns<sup>3</sup>. All safety concerns, as with other similar products containing colecalciferol, have been adequately reflected in the Summary of Product Characteristics (SPC)<sup>2</sup>.

Many of the potential adverse effects of vitamin D derive from its effects on calcium homeostasis, leading to hypercalcaemia. Excess vitamin D intake has been associated with cardiac toxicity and soft tissue calcification through hypercalcaemia<sup>24,25</sup>. The SPC states that caution is required in patients receiving treatment for cardiovascular disease. In addition, the SPC recommends that in preference to colecalciferol, other forms of vitamin D should be used in patients with severe renal insufficiency.

Fultium-D<sub>3</sub><sup>®</sup> contains arachis (peanut) oil and the SPC states that you should not use this medicinal product if you are allergic to peanut or soya<sup>2</sup>.

### 3.4 AWTTTC critique

- Fultium-D<sub>3</sub><sup>®</sup> is the only licensed colecalciferol preparation which does not contain calcium. All other licensed colecalciferol products contain calcium. Calcium supplementation may not be appropriate for all patients and the joint calcium/vitamin D formulations may have palatability issues<sup>8</sup>.
- No studies were submitted which specifically included Fultium-D<sub>3</sub><sup>®</sup>. The MHRA were satisfied that no new clinical or non-clinical efficacy studies were required to support the application for a licence, as the therapeutic use and safety profile of colecalciferol is well established<sup>3</sup>.

- Results from the meta-analyses should be interpreted with caution due to variability in study designs, methodological weaknesses in the studies included, addition of calcium in some trials and differences in the doses of vitamin D used. In addition there were differences in how vitamin D deficiency was defined.
- It is widely recommended that monotherapy should be used for the treatment of vitamin D deficiency; previously this could only be met with specials or unlicensed products<sup>3,6-10</sup>.
- Several unlicensed over-the-counter products which contain colecalciferol are available. The company submission and UK PAR highlight that these products contain inconsistent quantities of vitamin D<sup>1,3</sup>.

## **4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS**

### **4.1 Company submission**

The economic evidence provided by the company is limited to a simple budget impact analysis, undertaken on the assumption of cost minimisation, that all available formulations and brands of colecalciferol are therapeutically equivalent<sup>1</sup>. Fultium-D<sub>3</sub><sup>®</sup> 800 IU capsules are estimated by the company to be cost neutral or cost saving compared with alternative colecalciferol formulations. Assumptions underlying cost estimates are discussed below, with actual budget impact estimates discussed in Section 5.

#### **4.1.2 Company-reported cost estimates**

In the treatment of vitamin D deficiency, and subsequent maintenance, the acquisition cost of Fultium-D<sub>3</sub><sup>®</sup> 800 IU taken as four capsules daily (3,200 IU daily) for 12 weeks, followed by 800–1,600 IU daily for 40 weeks, is compared against that of colecalciferol 20,000 IU capsules taken three times weekly for 12 weeks, followed by 20,000 IU per month for nine months. The rationale provided by the company for the use of this comparator is that it appears to have the highest volume of use for this indication. The cost assumed for colecalciferol 20,000 IU capsules is based on a volume-weighted average of the net ingredient costs of Dekristol<sup>®</sup> (an unlicensed brand of colecalciferol 20,000 IU capsules imported from Germany) and other (generically prescribed) colecalciferol 20,000 IU capsules listed in Prescription Cost Analysis data for England, 2011<sup>26</sup>. Under this scenario, Fultium-D<sub>3</sub><sup>®</sup> 800 IU capsules are estimated to have an annual cost of £90.90 per patient, compared with £105.14 for colecalciferol 20,000 IU capsules; i.e. Fultium-D<sub>3</sub><sup>®</sup> 800 IU capsules are estimated to be cost saving by £14.24 per patient per year.

For use in insufficiency, prevention or as an adjunct to treatment of osteoporosis, direct substitution of Fultium-D<sub>3</sub><sup>®</sup> 800 IU daily for an equivalent dose of any licensed combined calcium/colecalciferol product is assumed. The company assumes the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU in these scenarios to be cost neutral, on the basis that the daily acquisition cost is the same as the lowest cost combination product when used at the equivalent colecalciferol dose.

#### 4.1.3 AWTTTC critique of the cost estimates

- The cost estimates presented by the company are based on the assumption of equivalence of Fultium-D<sub>3</sub><sup>®</sup> and other vitamin D<sub>3</sub> products. However, no evidence of equivalence appears to be available for any of the colecalciferol formulations and brands. Indeed, the company states that one of the advantages of Fultium-D<sub>3</sub><sup>®</sup> 800 IU capsules is the standardisation of their content, which it considers to be lacking for unlicensed formulations<sup>1</sup>.
- The assumed costs of the comparator for the treatment of deficiency are based on prescription costs analysis data for England from 2011<sup>26</sup>, which may not reflect the current acquisition costs of colecalciferol 20,000 IU capsules. The company reports in its submission a cost of £3 per capsule for Dekristol<sup>®</sup>, reportedly based on 2011 prices<sup>1</sup>, but in its budget impact model appears to have assumed a base case cost per Dekristol<sup>®</sup> capsule of £1.67. Both of these estimates appear to be considerably greater than the costs of Dekristol<sup>®</sup> reported in an NHS review of available vitamin D products from April 2012, which indicates a range of supplier-dependent costs for 50 capsules ranging from £10.40 plus £6.50 handling charge, to £16.47 plus £14.45 handling charge<sup>27</sup>. The review of available vitamin D products also highlights a wide range of available products with varying acquisition costs<sup>27</sup>. The cost of the comparator may therefore have been overestimated by the company. Variation in the assumed costs of the comparator has been explored by the company in its budget impact analysis.
- There appears to be a wide range of dose regimens recommended for the treatment of vitamin D deficiency across different NHS trusts<sup>6</sup>. The comparator dose regimen assumed by the company appears compatible with some of the NHS trust recommendations.
- The company assumes the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU would be cost neutral compared with calcium–colecalciferol combination products when used as an adjunct to the treatment of osteoporosis; however, this would only be the case if calcium supplementation is not indicated or required.

## 5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

The budget impact analysis relates to the treatment of deficiency of vitamin D (and subsequent maintenance), and assumes the cost savings with the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU estimated by the company, as discussed in Section 4.0.

Data from a recent study of vitamin D<sub>3</sub> levels in over 2,200 adults in Scotland indicates 34.5% of adults have severe vitamin D deficiency<sup>28</sup>. Applying this proportion to Welsh adult population estimates equates to 866,208 adults in Wales with severe deficiency. Using a wide range of sources, the company estimates that 11.4% would have contraindications to treatment with Fultium-D<sub>3</sub><sup>®</sup> (e.g. allergy to arachis [peanut] oil, severe renal impairment, hypercalcaemia, which also may apply for other colecalciferol formulations). Therefore, the remaining 88.6% would be potentially eligible for treatment. Of these, 0.36% are assumed to receive Dekristol<sup>®</sup>, which appears to be based on estimates of prescribing rates in England. All are assumed to receive Fultium-D<sub>3</sub><sup>®</sup> 800 IU instead of Dekristol<sup>®</sup>. Therefore, the company estimates 2,702 patients will receive Fultium-D<sub>3</sub><sup>®</sup> 800 IU in year 1, rising to 2,754 in year 5.

### 5.1.2 Results

In its base case analysis, the company estimates Fultium-D<sub>3</sub><sup>®</sup> 800 IU to be cost saving, by £14.24 per treated patient per year. Across all patients estimated to receive Fultium-D<sub>3</sub><sup>®</sup> 800 IU, the company anticipates cost savings of around £38,500 to £39,200 in each of the next five years.

Sensitivity analyses (around year 1 estimates) indicate that budget impact estimates are sensitive to the assumed costs of Fultium-D<sub>3</sub><sup>®</sup> 800 IU and the comparator: a 20% increase in the cost of Fultium-D<sub>3</sub><sup>®</sup> 800 IU results in additional costs of £10,600 per year (rather than cost savings), and a 20% decrease in the cost of the comparator results in additional costs of around £18,300 per year<sup>1</sup>. Supplementary analyses provided by the company explore the impact of the assumed daily dose of Fultium-D<sub>3</sub><sup>®</sup> following the first 12 weeks of treatment. These indicate that when the cost of the main comparator (Dekristol<sup>®</sup>) is assumed to be in the range £1.60 to £1.85, the use of Fultium-D<sub>3</sub><sup>®</sup> at a dose of 800 IU daily for 40 weeks results in cost savings of £73,800 to £139,800 per year; however, the use of Fultium-D<sub>3</sub><sup>®</sup> at a dose of 1600 IU daily for 40 weeks results in additional costs of £18,500 to £84,400.

### 5.1.3 AWTC critique of the budget impact analysis

- In the absence of robust Welsh-specific data, the company has made reasonable efforts to describe the epidemiology of vitamin D deficiency in Wales, and has undertaken sensitivity analyses to explore the impact of key assumptions on the epidemiology and costs of treatment.
- The model only considers the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU for vitamin D deficiency. Although the company estimates Fultium-D<sub>3</sub><sup>®</sup> 800 IU to be cost neutral in other uses (e.g. adjuvant treatment of osteoporosis), this would depend on the clinical need of patients for calcium supplementation. The potential for additional calcium supplementation costs is not considered in any scenarios; however, the company also notes that Fultium-D<sub>3</sub><sup>®</sup> is intended for use where calcium supplementation is not required. The availability of a licensed vitamin D product could potentially reduce unnecessary exposure to calcium in those in whom it is not clinically indicated.
- The uncertainties in cost estimates discussed in section 4.1.3 apply to the costs assumed in the budget impact estimates. In particular, the uncertainties in assumed costs of comparators are important, given the sensitivity analyses that demonstrate a 20% reduction in the assumed comparator costs results in additional costs (of £18,300 per year) from the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU rather than cost savings. Based on the costs of Dekristol<sup>®</sup> reported in an NHS review of available vitamin D products from April 2012<sup>27</sup>, the company-assumed acquisition costs of colecalciferol 20,000 IU capsules may be overestimated by more than 20%.
- Collectively, the company's estimates of costs savings with the use of Fultium-D<sub>3</sub><sup>®</sup> 800 IU capsules appear subject to significant uncertainty.

### 5.2 Comparative unit costs

Comparative unit costs are difficult to provide due to differences in licensed indications, dose formulations and recommended doses. A wide range of products are available containing colecalciferol or ergocalciferol, many combined with calcium. Table 1 includes example 30-day acquisition costs for providing 800 IU of colecalciferol (or ergocalciferol) using branded products listed in the current Drug Tariff (June 2012)<sup>29</sup>. These are necessarily illustrative only. Unlicensed specials-manufactured oral solutions providing colecalciferol 3,000 IU per ml and ergocalciferol 3,000 IU per ml have current Drug Tariff list prices of £102.70 per 100 ml bottle and £208.44 per 60 ml bottle, respectively. The price for Dekristol<sup>®</sup> 20,000 IU capsules (used as a comparator

in the current submission), and other oral liquid formulations, are not listed in the usual published sources. A recent NHS review of available vitamin D products indicates a range of supplier-dependent costs for 50 Dekristol<sup>®</sup> capsules ranging from £10.40 (plus £6.50 handling charge), to £16.47 (plus £14.45 handling charge)<sup>27</sup>.

**Table 1. Example acquisition costs of products containing vitamin D**

Product/formulation	Dose required to provide equivalent to 800 IU colecalciferol	Example 30-day cost per patient per 800 IU colecalciferol
Fultium-D <sub>3</sub> <sup>®</sup> (colecalciferol 800 IU) capsules	1 capsule	£1.80
Accrete D <sub>3</sub> <sup>®</sup> (colecalciferol 400 IU/calcium carbonate 1.5 g) tablets	2 tablets	£1.80
Adcal D <sub>3</sub> <sup>®</sup> (colecalciferol 400 IU/calcium carbonate 1.5 g) chewable tablets	2 tablets	£1.96
Calcichew D <sub>3</sub> <sup>®</sup> Forte (colecalciferol 400 IU/calcium carbonate 1.25 g) chewable tablets	2 tablets	£4.25
Kalcipos-D <sup>®</sup> (colecalciferol 800 IU/calcium carbonate 1.25 g) chewable tablets	1 tablet	£4.21
Calfovit D <sub>3</sub> <sup>®</sup> (colecalciferol 800 IU/calcium phosphate 3.1 g) effervescent granule sachets	1 sachet	£4.32
Calcium and ergocalciferol (non-proprietary) (calcium lactate 300 mg/calcium phosphate 150 mg/ergocalciferol 400 IU tablets)	2 tablets	£17.36

*Costs are based on eDrug Tariff list prices as of 22 June 2012<sup>29</sup>. This table does not imply therapeutic equivalence of formulations or the stated doses. All relevant Summaries of Product Characteristics should be consulted for full licensed indications and dosing details<sup>2,30-34</sup>.*

## 6.0 ADDITIONAL INFORMATION

### 6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, Fultium-D<sub>3</sub><sup>®</sup> is appropriate for prescribing by all prescribers within NHS Wales for the above indication.

### 6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

### 6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

### 6.4 Evidence search

**Date of evidence search:** 7 June 2012

**Date range of evidence search:** No date limits were applied to database searches.

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