

colecalfiferol 800 international units (equivalent to 20 micrograms vitamin D<sub>3</sub>)  
capsules (Fultium-D<sub>3</sub>®) SMC No. (801/12)

## Internis Pharmaceuticals Limited

10 August 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**colecalfiferol (Fultium-D<sub>3</sub>®)** is accepted for use within NHS Scotland.

**Indication under review:** In adults, the elderly and adolescents for the prevention and treatment of vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

The therapeutic use and safety profile of colecalciferol as a treatment for vitamin D deficiency and as an adjunctive treatment in osteoporosis is well established. There are no comparative data for Fultium-D<sub>3</sub>® as it is the first licensed oral vitamin D monotherapy formulation.

Overleaf is the detailed advice on this product.

**Vice Chairman,  
Scottish Medicines Consortium**

## Indication

The prevention and treatment of vitamin D deficiency. As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency. Fultium-D<sub>3</sub>® is indicated in adults, the elderly and adolescents.

## Dosing Information

For vitamin D deficiency in adults and the elderly (serum levels <25nmol/L (<10ng/mL): one to four capsules (800 to 3,200 international units [IU]) daily for up to 12 weeks dependent upon the severity of the disease and the patient's response to treatment.

For vitamin D insufficiency in adults and the elderly (serum levels 25 to 50nmol/L [10 to 20ng/mL]) and long term maintenance therapy following treatment of deficiency in adults and the elderly and prevention of vitamin D deficiency: one to two capsules (800 to 1,600 IU) daily.

For 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.

As an adjunct to specific therapy for osteoporosis: one capsule daily.

The capsules should be swallowed whole (not chewed) with water.

Fultium-D<sub>3</sub>® should only be given under medical supervision and should not be used in children under 12 years.

## Product availability date

30 January 2012

## Summary of evidence on comparative efficacy

Fultium-D<sub>3</sub>® was granted marketing authorisation following the submission of an abridged bibliographic application based on the well established use of its active constituent, colecalciferol (vitamin D<sub>3</sub>). The Medicines and Healthcare Products Regulatory Agency (MHRA) did not require the submission of any clinical studies specifically using Fultium-D<sub>3</sub>®. It is the first oral vitamin D monotherapy preparation to be licensed in the UK. Vitamin D is essential to maintain skeletal calcium balance by promoting intestinal calcium absorption, osteoclast-mediated bone resorption, and maintenance of serum calcium and phosphate levels.

The Fultium-D<sub>3</sub>® formulation of colecalciferol has not been evaluated in clinical studies; however, the submitting company cited two small studies demonstrating increased vitamin D levels with the use of colecalciferol.

Colecalciferol was compared with ergocalciferol (vitamin D<sub>2</sub>) in a randomised controlled study when both were administered at doses of either 1,600 IU daily or 50,000 IU monthly for one year in 64 people aged ≥65 years. Colecalciferol was modestly, but significantly, more effective than

ergocalciferol in increasing serum 25-hydroxyvitamin D (25[OH] D) although in around 20% of individuals levels of 25(OH) D did not increase above 30ng/mL despite good compliance.<sup>1</sup>

A randomised controlled study in the United States of America compared colecalciferol 2,000 IU daily for six months with placebo in 46 army veterans aged  $\geq 70$  years. Efficacy results were reported only for the 34 participants who completed the study, 17 in each group. In the treatment group, mean serum 25(OH) D increased from  $28.4 \pm 7.9$  ng/mL at baseline to  $42.7 \pm 10.5$  ng/mL after six months, but levels remained less than 32 ng/mL in 18% (3/17) participants. In the placebo group, the baseline level of  $27.7 \pm 8.3$  ng/mL did not change significantly after six months ( $28.8 \pm 8.7$  ng/mL). The authors suggested that, in older people, treatment with colecalciferol 2,000 IU daily for six months is generally safe and corrects low levels of vitamin D in most but not all individuals.<sup>2</sup>

Several recent meta-analyses of outcomes of vitamin D supplementation in different populations have been published. A Cochrane meta-analysis of ten studies in frail elderly people living in institutions compared vitamin D monotherapy with placebo or no treatment and found no decrease in risk of fracture.<sup>3</sup> Patient-level pooled analysis of 68,500 patients from seven major vitamin D fracture studies in the United States of America and Europe found that although combined calcium and vitamin D treatment reduced hip fractures and total fractures, vitamin D alone did not reduce fracture risk.<sup>4,5</sup>

A meta-analysis of eight randomised controlled studies in a total of 2,426 people with or without concomitant calcium supplements concluded that supplemental vitamin D in a daily dose of 700 to 1,000 IU reduced the risk of falling among older individuals by 19%.<sup>6</sup>

A meta-analysis of 57,311 participants in 18 randomised controlled studies investigated the effect of vitamin D supplementation on mortality. Some studies also included calcium in one or both arms. A total of 4,777 deaths from any cause occurred during an adjusted mean observation time of 5.7 years. Doses of vitamin D supplements varied from 300 to 2,000 IU daily and the adjusted mean daily dose was 528 IU. In nine studies there was a 1.4 to 5.2-fold difference in serum 25 (OH) D concentration between the intervention and control groups. The summary relative risk (RR) for mortality from any cause was 0.93 (95% CI: 0.87 to 0.99) and was reported to be independent of the addition of calcium supplements in the intervention. The authors suggested that there was an association between intake of ordinary doses of vitamin D supplements and reduction in total mortality rates.<sup>7</sup> This finding is supported by a 2011 Cochrane systematic review that assessed the beneficial and harmful effects of vitamin D for prevention of mortality in adults in high income countries. Over 94,000 individuals in 50 studies were randomised to receive vitamin D (D2, D3, alfacalcidol or calcitriol at any dose, duration, and route of administration) or placebo/no treatment. Participants could also be receiving calcium supplements. Almost 80% of participants were female, the mean age was 74 years and the median treatment duration was two years. When the different forms of vitamin D were assessed separately, only vitamin D3 decreased mortality significantly (RR 0.94, 95% CI 0.91 to 0.98, 74,789 participants, 32 studies).<sup>8</sup>

## Summary of evidence on comparative safety

The safety profile of colecalciferol is well established and the MHRA stated in the United Kingdom Public Assessment Report (UKPAR) that no new or unexpected safety concerns arose from this application for marketing authorisation.<sup>9</sup>

Excess vitamin D intake may lead to hypercalcaemia and hypercalciuria and moderate levels (25 to 50 micrograms daily) may enhance renal stone formation in predisposed individuals. Vitamin D should be used with caution in patients with impaired renal function and calcium and phosphate levels should be monitored.

## Summary of clinical effectiveness issues

The clinical consequences of severe vitamin D deficiency include rickets in children and osteomalacia in adults. The main source of vitamin D for the general population is sunlight. Geographical, environmental, dietary and lifestyle factors contribute to a significant proportion of the Scottish population having low levels of vitamin D. In recent years there has been an increased awareness of the potential requirement for vitamin D supplementation in at-risk groups in the UK population which include: all pregnant and breastfeeding women; children under 5 years of age, older people aged 65 years and over; people who have low or no exposure to the sun; and people who have darker skin whose bodies are not able to make as much vitamin D as lighter-skinned people.

Fultium-D<sub>3</sub>® is the first oral vitamin D monotherapy product in the UK to receive a marketing authorisation and this was granted on the basis of well established use.

Most randomised, controlled studies of vitamin D supplementation have focussed on skeletal outcomes. As the majority of these studies involve the concomitant use of calcium supplements, it is not possible to distinguish those effects attributable specifically to vitamin D. There is some evidence that colecalciferol treatment may prevent falls in the elderly but evidence for fracture prevention is inconsistent. Evidence that vitamin D supplementation reduces mortality is limited and inconclusive.

There is no Scottish or UK guideline for the treatment of vitamin D deficiency using vitamin D monotherapy. The Scottish Government has published advice recommending the use of low dose colecalciferol (adult dose 400 IU daily), without measuring vitamin D levels, to prevent vitamin D deficiency in certain groups of the general population considered to be at risk. This dose recommendation is lower than the Fultium-D<sub>3</sub>® capsule strength.

Treatment with Fultium-D<sub>3</sub>® is dependent on the serum level of 25-hydroxyvitamin D (25[OH] D). This is the best indicator of overall vitamin D status as it reflects the total vitamin D from dietary intake, sunlight exposure, and the conversion of vitamin D from adipose stores in the liver. However, there is no standard method of measuring 25(OH) D status and different tests can produce very different results. The definition of vitamin D deficiency is generally accepted as a serum 25(OH) D level of <25 nmol/L but there are conflicting views on whether this should be the threshold for active treatment or whether the presence of osteomalacia is required. The term 'insufficiency' is used in the summary of product characteristics (SPC) for Fultium-D<sub>3</sub>® to indicate 25(OH) D levels between 25 and 50nmol/L but there is no clear consensus on whether treatment is warranted in this population.

Current treatment options are unlicensed and include imported medicines, 'specials' and nutritional supplements bought by patients on the advice of a healthcare professional. There is no agreement on the use of loading doses and doses currently used are highly variable. Fultium-D<sub>3</sub>® is only available on prescription. In the economic analysis submitted by the company, Fultium-D<sub>3</sub>® has been compared with Dekristol® (colecalciferol 20,000 IU capsules), which is licensed in Germany. It is an appropriate comparator for the treatment of vitamin D deficiency as clinical experts consulted by SMC have advised that Dekristol®, usually taken weekly or monthly, is currently used in Scotland. It was the most frequently prescribed colecalciferol preparation in England in 2011 according to prescription cost analysis.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has recently alerted healthcare professionals to a safety issue in relation to the colecalciferol content of an unlicensed vitamin D product, as the content was substantially greater than that stated on the product labelling.<sup>10</sup>

The availability of a licensed preparation of colecalciferol has advantages over current treatment options.

Fultium-D<sub>3</sub>® may be useful when patients require supplements of vitamin D but not calcium, or when calcium may be detrimental (due to intolerance or the risk of adverse effects), or when adherence to treatment is reduced due to the calcium component (usually related to large tablet size or chalky taste). The availability of a vitamin D monotherapy would also provide dosing flexibility compared with fixed dose calcium and vitamin D combination medicines. Fultium-D<sub>3</sub>® is a prescription only medicine ensuring that treatment may be monitored to prevent hypercalcaemia.

Fultium-D<sub>3</sub>® has a relatively narrow dose range (800 IU to 3,200 IU daily) which makes it less suitable for prevention of vitamin D deficiency in the at risk groups that should be targeted according to advice from the Scottish Government, and may be inappropriate for patients who require very high doses. Fultium-D<sub>3</sub>® is not licensed for use in children below 12 years of age. It is contra-indicated in patients allergic to peanuts or soya.

Clinical experts consulted by SMC advised that there is an unmet need for a licensed vitamin D monotherapy product to treat patients with vitamin D deficiency including those undergoing osteoporosis treatment, patients intolerant of calcium and those with osteomalacia.

## Summary of comparative health economic evidence

The submitting company presented several cost minimisation analyses for the following scenarios:

- 1) Treatment of vitamin D deficiency and maintenance in adults and the elderly, a comparison versus Dekristol®. Dosing of Fultium-D<sub>3</sub>® was assumed to be four capsules daily in the 12 week treatment phase followed by either (a) one capsule daily or (b) two capsules daily in the 40 week maintenance phase.
- 2) Treatment of insufficiency and prevention in adults and the elderly, a comparison versus either (a) combination calcium and colecalciferol tablets or (b) Dekristol®. The comparator would be Dekristol® if two Fultium-D<sub>3</sub>® capsules daily would have been required as maintenance therapy.
- 3) As adjunctive treatment for osteoporosis in adults and the elderly, a comparison with a combination calcium and colecalciferol tablet. The dose of Fultium-D<sub>3</sub>® was one capsule daily.
- 4) Treatment of deficiency or insufficiency in adolescents, a comparison with daily colecalciferol 10000 IU liquid (Zymad®). The dose of Fultium-D<sub>3</sub>® was one capsule daily.

A one year time horizon was used for all analyses.

The analysis compared the annual cost per patient of Fultium-D<sub>3</sub>® with those of the comparator treatments, and included medication costs only. The results for the six scenarios referred to above are shown in the table below:

Scenario	Indication	Comparator	Annual cost	
			Fultium-D <sub>3</sub> ®	Comparator
<b>1a</b>	Deficiency & maintenance	Dekristol®	£73.92	£105.14
<b>1b</b>			£107.52	£105.14
<b>2a</b>	Insufficiency and prevention	Combination calcium+colecalciferol	£43.80	£43.80
<b>2b</b>		Dekristol®	£87.60	£43.20

<b>3</b>	As an adjunct to treatment of osteoporosis	Combination calcium+colecalciferol	£43.80	£43.80
<b>4</b>	Deficiency or insufficiency in adolescents	Colecalciferol 10,000 IU liquid (Zymad)®	£43.80	£322.56

The results indicated that Fultium-D<sub>3</sub>® would be the preferred treatment on cost-minimisation grounds except in scenarios 1b and 2b.

A number of limitations or uncertainties were noted with the analysis. NDC had concerns that there was an untreated cohort of patients for whom the appropriate comparator would be no treatment and this has not been addressed in the submission. The cost of Dekristol® may vary from the £1.88 per capsule assumed by the company: the acquisition costs across NHS Scotland may in some cases be lower and this would affect the results of the cost-minimisation analysis. Despite these limitations, the economic case was considered demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

The Scottish Government published an advice statement in September 2010 with recommendations for the prevention of vitamin D deficiency in “at risk” groups. These include all pregnant and breastfeeding women; children under 5 years of age, older people aged 65 years and over; people who have low or no exposure to the sun; and people who have darker skin whose bodies are not able to make as much vitamin D as lighter-skinned people. The recommended adult daily dose of vitamin D is 10 micrograms (400 IU) vitamin D which cannot be delivered using Fultium-D<sub>3</sub>® 800 IU capsules.

## Additional information: comparators

No licensed preparation of colecalciferol as monotherapy is currently available. Comparators of Fultium-D<sub>3</sub>® include unlicensed vitamin D products that are imported or manufactured as ‘specials’ eg Dekristol® 20,000 IU colecalciferol capsules.

Licensed combinations of vitamin D and calcium are available for people who require both components. The MHRA notes in the UKPAR for Fultium-D<sub>3</sub>® that it is for use in those patients who have adequate calcium intake and therefore are only suffering from vitamin D deficiency. The combination product containing the highest colecalciferol and the least calcium content is included in the table below: 500mg calcium (as calcium carbonate) plus 20 micrograms (800 IU) colecalciferol (Kalcipos®).

## Cost of relevant comparators

Drug	Dose regimen for treatment of vitamin D deficiency in adults	Cost per 400 international units (IU) vitamin D3 (£)	Cost per 12 weeks (£) #
<b>Colecalciferol monotherapy</b>			
<b>Fultium-D<sub>3</sub>®</b>	<b>Orally 800 to 3,200 IU daily</b>	<b>0.06</b>	<b>10 to 40</b>
Dekristol®*	Orally 20,000 IU one to three times weekly	0.010 to 0.017**	5.76 to 31
<b>Colecalciferol plus calcium combination therapy</b>			
Kalcipos-D®***	Orally 800 IU daily****	0.07	12

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 23 May 2012. # A 12 week period was cited by the submitting company for treatment of deficiency

\*Dekristol® is not licensed in the UK. The dose regimen in the table is based on expert comments and the company submission, but other regimens are also used. \*\* Range of costs reported in Scotland, (excludes carriage costs); cost range over 12 weeks takes into account dose range and variable cost. \*\*\*Kalcipos-D® is not a direct comparator as it also contains calcium. \*\*\*\* Dose is for colecalciferol component; the licensed dose is one tablet daily.

## Additional information: budget impact

Due to the variability in acquisition costs of unlicensed vitamin D preparations in current clinical use it is difficult to quantify the likely budget impact of colecalciferol (Fultium-D<sub>3</sub>®).

Adjunct to specific therapy for osteoporosis:

The submitting company estimated the population eligible for treatment to be 129,779 in year 1, rising to 132,621 in year 5 with an estimated uptake rate of 100% in both years. The gross impact on the medicines budget was estimated to be £5.7m in year 1 and £5.8m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to result in savings of £1.7m in year 1 and £2.9m in year 5. Given the findings presented in scenario 3 of the economic analysis (cost equivalence between Fultium-D<sub>3</sub>® and the combination product that would be displaced), it would seem more likely that the budget impact will be cost neutral rather than cost saving. The submitting company has been asked to confirm this.

Treatment and maintenance of vitamin D deficiency:

The submitting company estimated the population eligible for treatment to be 4,709 in year 1 and rising to 4,811 year 5 with an estimated uptake rate of 100% in both years. The gross impact on the medicines budget was estimated to be £348k in year 1 and £356k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £147k in year 1 and £150k in year 5. It should be noted that these figures assume a cost of £1.88 per capsule for Dekristol®, which may in some cases be higher than the price paid in NHS Scotland. As such, the estimated cost savings may not be realised and a net budget impact is more likely.

## References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Binkley N, Gemar D, Engelke J et al. Evaluation of ergocalciferol or cholecalciferol dosing, 1,600IU daily or 50,000 IU monthly in older adults. Journal Clinical Endocrinology and Metabolism 2011; 96:981-8
2. Cherniack EP, Florez HJ, Hollis BW et al. The response of elderly veterans to daily vitamin D3 supplementation of 2,000 IU: A pilot efficacy study J Am Geriatr Soc 2; 59: 286–90.
3. Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews 2009, Issue 2.
4. The DIPART (vitamin D Individual Patient Analysis of Randomized Trials) group. Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe BMJ 2010 340 b5463
5. The DIPART (vitamin D Individual Patient Analysis of Randomized Trials) group. Correction to Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe BMJ 2010 340 b5463 BMJ 2011 343 d5245 (correction)
6. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials BMJ 2009; 339: b3692
7. Autier P, Gandini S Vitamin D supplementation and total mortality. Arch Intern Med 2007; 167:1730-7.
8. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database of Systematic Reviews 2011, Issue 7.
9. The Medicines Health and Regulatory Authority (MHRA) United Kingdom Public Assessment Report. Colecalciferol (Fultium-D<sub>3</sub>®). October 2011, PL17871/0151. [www.mhra.gov.uk](http://www.mhra.gov.uk)
10. The Medicines Health and Regulatory Authority (MHRA) Drug Alert, Company-Led Drug Recall: Dekristol/Dekristol capsules – Jumbogate Ltd. (Quvera Livery – CLDA(12)A/10) <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/DrugAlerts/Company-ledrecalls/CON172253>

This assessment is based on data submitted by the applicant company up to and including 06 July 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*