Submission for Vitamin D

Part A
1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Vitamin D [includes vitamin D3, colecalciferol (alternative spelling cholecalciferol) and vitamin D2, ergocalciferol (alternative name calciferol)].

2. Proprietary name(s).

Not applicable.

3. Name of the company / organisation / individual requesting a reclassification.

Not applicable. This request is made on behalf of the natural health products industry.

4. Dose form(s) and strength(s) for which a change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

5. Pack size and other qualifications.

Not applicable. This request is made on behalf of the natural health products industry.

6. Indications for which change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

7. Present classification of the medicine.

At the present time, Vitamin D is:

- Unscheduled when in products for external use.
- Unscheduled when in products for internal use containing 25 micrograms or less per recommended daily dose [ie equivalent to 1000 IU or less].
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

8. Classification sought.

It is proposed that the classification of Vitamin D is changed to:

- Unscheduled when in products for external use.
- Unscheduled when in products for internal use containing 75 micrograms [ie 3000 IU] or less per recommended daily dose.
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia
Vitamin D is:

- Unscheduled when in products for external use.
- Unscheduled when in products for internal use containing 25 micrograms or less per recommended daily dose.
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

Canada
Vitamin D is:

- Unscheduled in in oral dosage form containing 1,000 International Units [ie equivalent to 25 micrograms] of Vitamin D per dosage form or less, or where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by the person of less than 1,000 International Units of Vitamin D.
- Prescription drug in oral dosage form containing more than 1,000 International Units of Vitamin D per dosage form or, where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by the person of more than 1,000 International Units of Vitamin D.

UK
Vitamin D is a pharmacy medicine above 10 micrograms [or 400 IU].
Below this, Vitamin D is unscheduled.

USA
In the USA, many vitamin D products are marketed as dietary supplements which do not have to undergo a pre-approval process. There are at least 5,000 products containing Vitamin D on the US market. The vitamin content of these products ranges from 400 IU to 5000 IU (125 micrograms vitamin D).

10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.

Not applicable. This request is made on behalf of the natural health products industry.

11. Labelling or draft labelling for the proposed new presentation(s).

Not applicable. This request is made on behalf of the natural health products industry.

12. Proposed warning statements if applicable.

When used as an active ingredient in oral or sublingual products:

Vitamins can only be of assistance if the dietary vitamin intake is inadequate [OR]
Vitamin supplements should not replace a balanced diet.

These are the same statements currently used in Australian for products containing Vitamin D.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Manufacturers of current dietary supplement-type products will likely increase the quantity of Vitamin D in their products, or change their dosing instructions to deliver the maximum dose.

It should be noted that all dietary supplement products will be regulated under the NHP Bill. When the NHP Bill is passed, natural health products will have to be manufactured according to a Code of Manufacturing Practice.

Approved medicines containing Vitamin D as the active ingredient

Vitalipid N Adult emulsion for injection
Vitalipid N Infant emulsion for injection
Cernevit powder for injection

Products for injection are not permitted under the NHP regulatory scheme.

Caltrate with Vitamin D tablets	general sale
Calvid effervescent granules	general sale
Caltrate 600mg with 400 IU Vitamin D tablets	general sale
Elevit with Iodine tablets	pharmacy medicine
Fosamax Plus tablets	prescription medicine
Vit. D3 capsules	prescription medicine

It is possible that the sponsors of Caltrate with Vitamin D tablets, Calvid effervescent granules and Caltrate 600mg with 400 IU Vitamin D tablets may seek to re-position these medicines as natural health products. This will be possible when the NHP Bill comes into effect.

It is possible that the sponsors may seek to increase the dosage of these products.

The other medicines will not be affected by the proposed change:

- Elevit with Iodine tablets remains scheduled as a pharmacy medicine because of the iron component.
- Fosamax Plus remains scheduled as a prescription medicine because of the alendronate component.
- Vit. D3 capsules remains scheduled as a prescription medicine because of the very high content of colecalciferol (50,000 IU, or 1.25 mg).

Part B Reasons for requesting classification change including benefit-risk analysis.

Vitamin D was last considered by the Medicines Classification Committee at the 47th Meeting, 1 May 2012. A copy of the submission is attached as Appendix 1.

The minutes from the 47th Meeting are reproduced here.

Purpose

This was a Medsafe submission considering the reclassification of vitamin D, in tablets containing 1.25 mg of colecalciferol, from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults. The term "vitamin D" encompasses ergocalciferol (vitamin D2) and colecalciferol (vitamin D3). Both ergocalciferol and colecalciferol were considered part of this submission. The Committee were asked to consider:

- *Whether a pharmacist would have the necessary tools / support for diagnosing vitamin D deficiency in adults and for ongoing monitoring of the patient.*
- *Whether pharmacists would require training if down-scheduling was to occur.*
- *Whether the down-scheduling to restricted medicine should include doses taken monthly (up to 1.25 mg) or be restricted to those taken daily (e.g. up to 45 µg).*
- *Whether the down-scheduling should be linked to a limit on pack size (e.g. to a supply of three months).*
- *What warnings and precautions would need to be displayed on the labels (with any other warnings to appear in the package insert).*

The Committee were also given the Consensus Statement on Vitamin D and Sun Exposure in New Zealand, published online on 14 March 2012 (http://www.health.govt.nz/publication/consensus-statement-vitamin-d-and-sun-exposure-new-zealand).

The Committee noted there was one product currently marketed in New Zealand that would be affected by the proposed reclassification.

Background

At the 7th meeting on 31 July and 1 August 1990 ergocalciferol was classified as a prescription medicine (except in medicines containing 25 µg or less of ergocalciferol per daily dose) and vitamin D, its metabolites and derivatives, as prescription medicines (if the recommended daily dose exceeded 25 µg of vitamin D).

At the 37th meeting on 17 May 2007 it was recommended that the prescription medicine schedule entry for vitamin D should be amended to read 'for internal use in medicines containing more than 25 µg per recommended daily dose except in parenteral nutrition replacement preparations'.

At the 44th meeting on 2 November 2010, following the suggestion by a Committee member, it was recommended that Medsafe should make a submission proposing the reclassification of vitamin D, in tablets containing 1.25 mg or colecalciferol, from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults.

Vitamin D, ergocalciferol (vitamin D2) and colecalciferol (vitamin D3) are currently classified as:

- *prescription; for internal use in medicines containing more than 25 µg per recommended daily dose except in parenteral nutrition replacement preparations*
- *general sale; for external use; for internal use in medicines containing 25 µg or less per recommended daily dose; in parenteral nutrition replacement preparations.*

Comments

Seven pre-meeting comments were received during the consultation period.

Four supported the reclassification proposal and made the following comments:

a. *it is primarily the role of informed clinicians and pharmacists to establish the appropriate balance regarding access and protection against possible harms*
b. *the reclassification could improve access for specific patient groups at risk of vitamin D deficiency.*
c. *it may result in long term benefits not only to individuals but also to the New Zealand health system - implementation could result in more vitamin D treatment leading to reduced hospitalisations due to falls and fractures*
d. *appropriate advice and a limited number of tablets will minimise occurrence of inaccurate usage*
e. *benefits of vitamin D supplementation in the prevention and treatment of falls has been well documented*
f. *would be willing to develop guidance and training for pharmacists.*

Two suggested that, should reclassification occur, specific conditions would be required to ensure safe use of the product:

a. *the tracking of purchasers of vitamin D could prevent purchasers going from pharmacy to pharmacy to obtain vitamin D*
b. *purchasing tablets should be restricted to one tablet per month*
c. *a tracking procedure should be put in place to prevent individuals going from pharmacy to pharmacy so they can sustain much higher dose rates.*

Several submissions questioned the evidence presented in the application and pointed out that:

a. *the benefits of vitamin D supplementation may be overstated in the data analysis presented*
b. *harm from vitamin D supplementation may be understated*
c. *the existing body of research is unclear about the efficacy and safety of vitamin D*
d. *vitamin D deficiency in New Zealand may be less common than previously thought.*

Discussion

The Committee agreed that there was not enough evidence to support a reclassification to restricted medicine at this time and that the submission raised more questions than it answered. The literature presented was insufficient to demonstrate clear benefits from supplementation in the New Zealand population of interest, namely the frail elderly. The data was confounded by a number of factors including co-administration of calcium with vitamin D in some studies and contradictory in terms of risk and benefit.

It was agreed that 1.25 mg of colecalciferol per month was relatively safe and that, taken appropriately, the risk of harm was minimal. The risk that a patient could take more than one tablet per month, as monthly treatment is unusual, was noted. However, the Committee were more concerned that there was not enough evidence regarding the risk of long term use to support considering a change in classification.

Given the data presented and all the comments received during the consultation period, the Committee concluded that vitamin D, in tablets containing 1.25 mg of colecalciferol, should not be reclassified from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults.

Recommendation

That vitamin D, in tablets containing 1.25 mg of colecalciferol, should not be reclassified from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults.

This section should be supported by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim to help the maintenance of healthy teeth and bones with Vitamin D could be allowed.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

Vitamin D, calciferol, is a fat-soluble vitamin. It is found in food, but also can be made in the body after exposure to ultraviolet rays from the sun. Vitamin D exists in several forms, each with a different activity. Some forms are relatively inactive in the body, and have limited ability to function as a vitamin. The liver and kidney help convert vitamin D to its active hormone form.

The major biologic function of vitamin D is to maintain normal blood levels of calcium and phosphorus. Vitamin D aids in the absorption of calcium, helping to form and maintain strong bones. It promotes bone mineralization in concert with a number of other vitamins, minerals, and hormones. Without vitamin D, bones can become thin, brittle, soft, or misshapen. Vitamin D prevents rickets in children and osteomalacia in adults, which are skeletal diseases that result in defects that weaken bones.

Recommended intake
The RDA is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in each life-stage and gender

group. There is insufficient evidence to establish a RDA for vitamin D. Instead, an Adequate Intake (AI), a level of intake sufficient to maintain healthy blood levels of an active form of vitamin D, has been established. The 1998 AI level for vitamin D for adults, in µg and International Units (IUs) are:

Life-Stage	**Men**	**Women**
Ages 19-50	5 µg* or 200 IU	5 µg * or 200 IU
Ages 51-69	10 µg* or 400 IU	10 µg* or 400 IU
Ages 70 +	15 µg* or 600 IU	15 µg* or 600 IU

[1 µg vitamin D = 40 International Units (IU)]

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

Toxicity information

There is a high health risk associated with consuming too much vitamin D. Vitamin D toxicity can cause nausea, vomiting, poor appetite, constipation, weakness, and weight loss. It can also raise blood levels of calcium, causing mental status changes such as confusion. High blood levels of calcium also can cause heart rhythm abnormalities. Calcinosis, the deposition of calcium and phosphate in soft tissues like the kidney can be caused by vitamin D toxicity.

Consuming too much vitamin D through diet alone is not likely unless you routinely consume large amounts of cod liver oil. It is much more likely to occur from high intakes of vitamin D in supplements. The NZ Ministry of Health (National Health and Medical Research Council, 2006) considers an intake of 25 mcg (1,000 IU) for infants up to 12 months of age and 80 mcg (3,200 IU) for children, adults, pregnant, and lactating women to be the tolerable upper intake level (UL). Recommendations from the National Institutes of Health Office of Dietary Supplements (ODS, 2016) for RDA and UL are shown in italics:

Age group and gender		Vitamin D µg / day			
		AI	UL	*RDA*	*UL*
Infants	0-6 months	5	25 (1000 IU)	*10*	*25*
	7-12 months	5	25		*38*
Children	1-3 years	5	80 (3,200 IU)	*15*	*63*
	4-8 years	5	80		*75*
Boys	9-13 years	5	80	*15*	*100*
	14-18 years	5	80		
Girls	9-13 years	5	80	*15*	*100*
	14-18 years	5	80		
Men	19-30 years	5	80	*15*	*100*
	31-50 years	5	80		
	51-70 years	10	80		
	> 70 years	15	80	*20*	
Women	19-30 years	5	80	*15*	*100*
	31-50 years	5	80		
	51-70 years	10	80		
	> 70 years	15	80	*20*	
Pregnancy	14-18 years	5	80	*15*	*100*
	19-30 years	5	80	*15*	

	31-50 years	5	80		
Lactation	14-18 years	5	80	*15*	*100*
	19-30 years	5	80	*15*	
	31-50 years	5	80		

AI adequate intake
UL upper level of intake

It is immediately obvious that the AI levels recommended by the Ministry of Health are generally below those recommended by the National Institutes of Health.

Some researchers argue that the UL has been set too low: “Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations < 140 nmol/L, which require a total vitamin D supply of 250 µg (10,000 IU)/day to attain. Published cases of vitamin D toxicity with hypercalcaemia, for which the 25(OH)D concentration and vitamin D dose are known, all involve intake of ≥ 1000 µg (40,000 IU).” (Vieth, 1999). Indeed research with healthy adults has established that taking vitamin D3 daily at a dose of 100 µg (4000 IU) has been determined to be safe (Vieth, Chan, & MacFarlane, 2001). While earlier recommendations suggested much lower intakes, research over the last decade indicates that vitamin D can be tolerated at much higher doses. Indeed, sunshine can provide an adult with vitamin D in an amount equivalent to daily oral consumption of 250 µg (10,000 IU)/day, this is intuitively a safe dose (Vieth, 2007).

One of the concerns of excess vitamins D intake is hypercalcaemia. The weight of published evidence on toxicity shows that the lowest dose of vitamin D causing hypercalcaemia in some healthy adults is 1000 µg (40,000 IU)/day of the vitamin D2 form. Based on the evidence, Vieth concluded: “The overwhelming bulk of clinical trial evidence supports the conclusion that a prolonged intake of 250 µg (10,000 IU)/d of vitamin D3 likely poses no risk of adverse effects in almost all individuals in the general population” (Vieth, 2007).

Collectively, the absence of toxicity in trials conducted in healthy adults that used vitamin D dose > or = 250 µg/day (10,000 IU vitamin D3) supports the confident selection of this value as the UL (Hathcock, Shao, Vieth, & Heaney, 2007). Indeed many recent studies are using doses of vitamin D at 25,000 IU [or 625 mg/day].

Summary comment
In adults Vitamin D toxicity usually does not occur unless intakes exceed 50,000 IU per day. There have been a few cases of adverse reactions reported at daily intakes around 12,000 IU/day.

A proposed maximum daily dose 3000 IU (ie 75 micrograms) of Vitamin D is well within the [suggested] tolerable upper limit of 10,000 IU level.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Not applicable.

4. Relevant comparative data for like compounds.

Not applicable.

5. Local data or special considerations relating to New Zealand.

At this time the Medicines Schedule entry for Vitamin D is harmonised with Australia and Canada.
An increase in the allowed limit to 75 µg (or 3000 IU) will de-harmonise the Medicines Schedule with respect to these countries.

6. Interactions with other medicines.

The National Institutes of Health Office of Dietary Supplements states that vitamin D has the potential to interact with several medicines, such as corticosteroids and weight-loss drugs such as orlistat and cholestyramine (ODS, 2016).

7. Contraindications and precautions.

No information was provided by the applicant.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.
These have been reviewed in the previous submission to the MCC (Appendix 1). There is no new information to add.

10. Potential for abuse or misuse.
Vitamin D is not habit-forming or a drug of abuse. No potential for abuse or misuse is anticipated.

References

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Vieth, R., Chan, P.-C. R., & MacFarlane, G. D. (2001). Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. The American Journal of Clinical Nutrition, 73(2), 288-294.

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Appendix 1

SUBMISSION FOR RECLASSIFICATION OF VITAMIN D

Report prepared by Medsafe, December 2011

1. Reason for request

A member of the Medicines Classification Committee (MCC) had queried whether it would be appropriate to reclassify vitamin D, in tablets containing 1.25 mg colecalciferol, from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults.

The secretary of the MCC had written to the one sponsor company marketing this product in New Zealand asking if they would like to support the proposal. The company did not respond.

The matter was raised at the MCC's 44th meeting, where the Committee recommended that there was sufficient potential benefit in the proposal to warrant asking Medsafe to prepare a submission in the absence of industry support. The below submission is the outcome of that recommendation. It considers down-scheduling the classification of vitamin D from a prescription medicine to a restricted medicine, and at what strength and under what conditions this down-scheduling would be appropriate.

2. Present classification of vitamin D in New Zealand

The term "vitamin D" encompasses ergocalciferol (vitamin D_2) and colecalciferol (vitamin D_3). Both ergocalciferol and colecalciferol are to be considered as part of this submission, and both are currently classified as:

- Prescription - for internal use in medicines containing more than 25 µg per recommended daily dose except in parenteral nutrition replacement preparations
- General sale - for external use; for internal use in medicines containing 25 µg or less per recommended daily dose; in parenteral nutrition replacement preparations.

3. Classification status in other countries

Australia

Vitamin D is listed in Schedule 4 (Prescription Only Medicine) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for human internal therapeutic use except in preparations containing 25 µg or less of vitamin D per recommended daily dose.

The National Drugs and Poisons Scheduling Committee (NDPSC) reconsidered the classification of vitamin D at their 57th meeting in November 2009. An application had been received requesting that vitamin D be down-scheduled to Schedule 3 (Pharmacist Only) when for internal use in preparations containing more than 25 µg but not more than 125 µg of vitamin D per recommended daily dose. The NDPSC decided against this request on the basis that vitamin D deficiency cannot be diagnosed and managed in a pharmacy setting. It was deemed that a patient's medical practitioner would need to get involved as the diagnosis and ongoing management would require clinical laboratory monitoring of serum 25 hydroxy-vitamin D (25-OHD) levels.

UK

Vitamin D is listed as a General Sales List (GSL) medicine up to a maximum daily dose of 10 µg (400 IU). If present at levels greater than 10 µg, the product containing it will be a pharmacy medicine.

Canada

Vitamin D is listed in Schedule F to the Food and Drug Regulations, CRC, c 870 (Prescription medicine) in oral dosage forms containing more than 25 µg (1000 IU) of vitamin D per dosage form or, where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by that person of more than 25 µg of vitamin D.

US

As in New Zealand, many vitamin D products are marketed as dietary supplements. Dietary supplements do not undergo a pre-approval process.

There is also one approved drug (a capsule containing 1.25 mg ergocalciferol) registered with the FDA as a prescription medicine.

4. New Zealand products and current availability

Prescription medicines

In New Zealand, three approved medicines for oral use are currently marketed that contain more than 25 µg of vitamin D per dose.

Two of these medicines are combination products:

- Fosamax Plus 70/140 tablets (140 µg colecalciferol/dose form plus alendronate)
- Fosamax Plus 70/70 (70 µg colecalciferol/dose form plus alendronate)

Fosamax Plus is indicated for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended. The recommended dose is one tablet per week (i.e. 10 µg or 20 µg colecalciferol per day). Should colecalciferol be reclassified, Fosamax Plus products would remain prescription medicines by virtue of the alendronate component of these products.

The third product, Cal.D.Forte®, contains 1.25 mg (50,000 IU) of colecalciferol. The recommended long-term maintenance dose for Cal.D.Forte® is one tablet per month, equating to a dose of 40.3-41.7 µg (1613-1667 IU) colecalciferol per day for a month containing 30-31 days.

This dose is for more than just supplementing the diet, as illustrated by the:

- adequate intake values suggested by the Nutrient Reference Values (NRV) for Australia and New Zealand monograph for vitamin D (2006)
- recommended dietary allowance suggested by the United States' Institute of Medicine (IOM, 2011).

	NRV's recommended adequate intake	**IOM's recommended dietary allowance**
1-50 years	5 µg/day	15 µg/day
51-70 years	10 µg/day	15 µg/day
> 70 years	15 µg/day	20 µg/day

Indeed, the currently approved indications for Cal.D.Forte®, as stated in the data sheet, are as follows:

- Colecalciferol is indicated for treatment of vitamin D deficiency associated with malabsorption in children and/or adult patients.
- Colecalciferol is indicated for prevention and treatment of vitamin D deficiency states. Vitamin D deficiency may occur as a result of inadequate nutrition, intestinal malabsorption, or lack of exposure to sunlight, but does not occur in healthy individuals receiving an adequate balanced diet and exposure to sunlight.
- Requirements may be increased and / or supplementation may be necessary in the following persons or conditions (although clinical deficiencies are usually rare).
    - Alcoholism.
    - Dark-skinned individuals.
    - Hepatic-bilary tract disease – hepatic function impairment, cirrhosis, obstructive jaundice.
    - Infants, breast-fed, with inadequate exposure to sunlight.
    - Intestinal disease – celiac, tropical sprue, regional enteritis, persistent diarrhoea.
    - Lack of exposure to sunlight combined with reduced vitamin D intake.
    - Renal function impairment.
- In general, vitamin D absorption will be impaired in any condition in which fat malabsorption (steatorrhea) occurs.
- Some unusual diets, (eg, strict vegetarian diets with no milk intake such as vegan-vegetarian or macrobiotic, or reducing diets that drastically restrict food selection) may not supply minimum daily requirements of vitamin D. Supplementation may be necessary in patients receiving total parenteral nutrition (TPN) or undergoing rapid weight loss or in those with malnutrition, because of inadequate dietary intake.
- Congenital rickets have been reported in newborns whose mothers had low serum levels of vitamin D.

Cal.D.Forte® is distributed by the manufacturer in a 12 tablet pack, and was granted provisional consent in 2000. This provisional consent has been renewed in 2002, 2004, 2006, 2008 and in 2010.

Information on the date of original marketing of Cal.D.Forte® in New Zealand is not available. However, Cal.D.Forte® is fully subsidised by PHARMAC and has been funded by PHARMAC for over three years. PHARMAC's estimate of patients receiving Cal.D.Forte® is 171,390 for 2010 and 126,880 for 2009. (These patient usage data are not just limited to use in the prevention and treatment of vitamin D deficiency states in adults.) A significant proportion of patients were aged over 55 years; in 2010, 93,060 patients (54.3%) were aged 65 years and over, and 29,910 (17.5%) were aged 55-64 years.

Whether Cal.D.Forte's classification is affected by any down-scheduling of vitamin D depends on the strength and indications associated with the down-scheduling as well as any restrictions on daily versus monthly dosing. It is also noted that Cal.D.Forte is currently indicated for use in deficiency states in both adults and children, but this submission relates only to use in adults (particularly the elderly). Medsafe considers that children with vitamin D deficiency need to be placed under a doctor's care.

Over-the-counter medicines

A number of vitamin D-containing multivitamin/mineral products that are currently marketed have been approved as over-the-counter medicines for oral use. These include:

- Caltrate with vitamin D tablets (5 µg colecalciferol/dose form)
- Elevit tablets (12.5 µg colecalciferol/dose form)
- Elevit with Iodine tablets (12.5 µg colecalciferol/dose form)
- Karicare Vitadol C infant drops (11.67 µg colecalciferol/daily dose of 10 drops)

Any down-scheduling of vitamin D from prescription medicine to restricted medicine would not affect the classification status of these products.

5. Potency

Types of vitamin D

Vitamin D occurs in two forms. One is produced by the action of sunlight on skin (vitamin D_3 or colecalciferol) and the other is found in a limited range of foods (vitamin D_2 or ergocalciferol). Vitamin D in foods is fat soluble and is biologically less active. Its metabolite, 1,25-dihydroxyvitamin D (calcitriol) is the biologically active hormone responsible for its physiological actions. In the circulation vitamin D appears as 25-OHD, which is five times more potent than colecalciferol (NRV, 2006).

Colecalciferol and ergocalciferol are transferred to the liver where they are converted to 25-hydroxyvitamin D, which is then transferred to the kidneys and converted to 1,25-dihydroxy-vitamin D (Martindale, 2011).

1,25-dihydroxyvitamin D appears to act by binding to a specific receptor in the cytoplasm of the intestinal mucosa and subsequently being incorporated into the nucleus, probably leading to formation of the calcium-binding protein that results in increased absorption of calcium from the intestine. Also, 1,25-dihydroxyvitamin D may regulate the transfer of calcium ion from bone and stimulate reabsorption of calcium in the distal renal tubule, thereby effecting calcium homeostasis in the extracellular fluid (Cal.D.Forte data sheet).

There is minimal evidence to support one type of vitamin D supplementation over another. It has been suggested that active forms of vitamin D should be slightly more effective than vitamin D_2 or vitamin D_3, which require conversion in the kidneys to an active form. However, other studies show no such effects (Bjelakovic *et al*, 2011; Bischoff-Ferrari *et al*, 2009a). There has also been a suggestion that vitamin D_3 may be more effective than vitamin D_2 (Bjelakovic *et al*, 2011; Bischoff-Ferrari *et al*, 2009a; Armas *et al*, 2004) but, once again, this is not seen across all studies. Holick *et al* (2008) found that a daily dose of 25 µg (1000 IU) vitamin D_2 for 11 weeks was as effective as 25 µg vitamin D_3 in increasing serum 25-OHD levels.

No vitamin D_2 tablets are currently marketed as medicines in New Zealand. (Vitamin D_2 appears to be more commonly sold in North America, where it is present in the one FDA approved vitamin D prescription medicine.) Two active vitamin D products, containing alfacalcidol and calcitriol, and one vitamin D_3 product are fully subsidised by PHARMAC. However, active vitamin D products are much more expensive than the subsidised vitamin D_3 product (Pharmac, 2010). Several meta-analyses also suggest that the risk profile, particularly with regards to the development of hypercalcemia, is higher for the active forms (Bjelakovic *et al*, 2011; Gillepsie *et al*, 2009; Avenell *et al*, 2009; Bischoff-Ferrari *et al*, 2009a). For these reasons, vitamin D_3 and vitamin D_2 are the types under consideration here.

Dose

With regards to appropriate doses, a recently published meta-analysis of randomised controlled trials suggested that a high dose (700-1000 IU) of vitamin D was associated with a

19% reduction in risk of falling in people older than 65 years of age in stable health, within 2-5 months of treatment initiation. This benefit was not affected by gender, age, or type of dwelling (community or in nursing homes; Bischoff-Ferrari *et al*, 2009a).

Another meta-analysis by Bischoff-Ferrari *et al* (2009b) indicated that vitamin D doses of 482-770 IU/daily resulted in a 20% reduction in the relative risk of nonvertebral fractures and an 18% reduction in the relative risk of hip fractures. These benefits were not associated with lower doses of vitamin D.

It is interesting to note that these studies found evidence of improvement at vitamin D quantities that are currently unscheduled (i.e. up to 1000 IU or 25 µg per day), although the authors indicated that higher doses of vitamin D should be explored in order to optimise the benefit.

Dose regimen

Studies have generally assumed equivalency between taking a smaller dose of vitamin D once a day and taking a proportionally larger dose of vitamin D once a week or month. Chel *et al* (2007) investigated this in nursing home residents (338 participants, mean age of 84 years) who received vitamin D doses of either 600 IU/day, 4,200 IU/week or 18,000 IU/month for four months. Serum 25-OHD content increased from a mean baseline of 25 nmol/L to 62.5 nmol/L among those taking vitamin D daily, 67.2 nmol/L among those taking vitamin D weekly, and 53.1 nmol/L among those taking vitamin D monthly. The differences were significant across all treatments. The short nature of the study prevented the researchers from drawing any firm conclusions about the effect of the different regimens on fall and fracture rates

6. Benefit of vitamin D to individuals and the community

Older people are susceptible to a greater risk of falls and fractures due to age-related poor bone health and loss of muscle mass and tone. Up to 30% may fall each year. Although one in five falls may require medical attention, less than one in 10 results in a fracture (Gillespie *et al*, 2009).

Similar statistics are reported for New Zealand. According to the Accident and Compensation (ACC) website, falls are the cause of half of all ACC claims and costs in people aged 65 years and over. They account for 75% of injury-related hospital admissions. Depending on the population under study, between:

- 22-60% of older people suffer injuries from falls
- 10-15% suffer serious injuries
- 2-6% suffer fractures
- 0.2-1.5% suffer hip fractures.

Further break-down on falls data from the ACC and the University of Otago's Injury Prevention Research Unit (IPRU) can be found in Appendices 1 and 2.

This is of relevance to vitamin D supplementation as supplementation has been reported to have a direct beneficial effect on muscles, improving strength and balance in older persons (Bischoff-Ferrari *et al*, 2009a; Inderjeeth *et al*, 2007).

Also, elderly living in institutional care facilities or equivalent are generally considered to be at risk of vitamin D deficiency, and vitamin D deficiency is associated with a high incidence of fracture. When hip fractures occur in older people, they are significantly associated with excess mortality, morbidity and health and social service expenditure (Zang, 2007).

Other people who have been identified as being at high risk of vitamin D deficiency include people with skin conditions who have been advised to avoid sunlight, people with dark skin (particularly if veiled) and those people with vitamin D malabsorption (ANZMBS *et al*, 2005).

Several recent Cochrane reviews on the effect of vitamin D supplementation have been published. A 2011 review (Bjelakovic *et al*, 2011) analysed the influence of different forms of vitamin D on mortality. In the 50 trials a total of 94,148 participants were randomly assigned to either vitamin D or no treatment or a placebo. The mean age of participants was 74 years and the mean proportion of women was 79%. The median duration of vitamin D administration was two years. The authors reported that vitamin D_3 reduces mortality by about 6%, corresponding to 200 participants that need to be treated over a median of two years to save one additional life. The authors found evidence that vitamin D_3 decreases mortality in predominantly elderly women who are mainly in institutions and dependent care.

Another Cochrane review (Avenell *et al*, 2009) examined the evidence for vitamin D and related vitamin D compounds in preventing fractures resulting from osteoporosis in older people. Eight trials (totalling 46,658 participants) were included in the analysis, with the authors concluding that vitamin D taken with additional calcium supplements does appear to reduce the risk of hip fractures in people living in institutional care. Vitamin D alone (nine trials, 24,749 participants) appeared unlikely to be effective in preventing hip fractures. The DIPART group (2010) pooled the data of seven vitamin D fracture trials (totalling 68,500 participants) and found similar results to Avenell *et al* (2009) for vitamin D alone compared to vitamin D with calcium supplementation, as did an ACC literature review (Zang, 2007). Most of the studies using vitamin D only involved daily intakes equating to 10-25 µg. There was no discussion of whether higher daily intakes would have an effect on fractures.

Research has also been conducted on the influence of vitamin D supplementation on falls. One Cochrane review (Cameron *et al*, 2010) examined this in older people in nursing care facilities and hospitals. Vitamin D supplementation was shown to be effective in reducing the rate of falls in nursing care facilities (four trials, 4,512 participants), although the results also showed large heterogeneity (I^2=62%). A related Cochrane review (Gillepsie *et al*, 2009) found that, overall, vitamin D did not reduce the rate of falls in older people living in the community (13 trials, 23,112 participants) although limited data suggested that there may be some benefit to people with lower vitamin D levels. A literature review by ACC found similar differences for people in the community versus those in long-term and hospital care (Robertson & Campbell, 2008). Pooled results from thirteen studies (23,000+ participants) also showed no benefit of vitamin D supplementation on fall prevention (Holick, 2007).

Thus, the benefit of such supplementation on community-dwelling older people is less clear. The Gillepsie *et al* study suggests it may be of benefit to a subgroup in the community (those with low serum vitamin D levels) but acknowledges that insufficient data are available to draw a firm conclusion. Pooling the results of multiple studies may also mask or outweigh any benefit of the different type (e.g. vitamin D_2 vs. vitamin D_3, etc), dose, dose regimen or route of administration of vitamin D used. For instance, Bischoff-Ferrari *et al* (2009a) analysed data from eight trials (totalling 2,426 participants) and found a significant effect on the risk of falls in both ambulatory and institutionalised older individuals, but only at daily vitamin D doses of above 700 IU/day. The issue of vitamin D type and dose is discussed in further detail in the potency section of this report.

While vitamin D deficiency in Aged Residential Care (ARC) residents has been well recognised, the prevalence of vitamin D deficiency in community-dwelling older people has only recently become better known. It has been estimated that 40-100% of elderly American and European men and women are deficient in vitamin D (Holick, 2007).

Vitamin D insufficiency is common in the New Zealand population. An analysis of data from the 1997 National Nutrition Survey of New Zealand found that 2.8% of individuals aged 15 years or older had serum levels below 17.5 nmol/L, while 27.6% had levels below 37.5 nmol/L (NRV, 2006). Seasonal fluctuation exists, with serum vitamin D concentrations lowest in spring and highest in summer. Ethnicity differences also exist, with Pacific and Māori people having lower serum vitamin D concentrations compared with European and other, fair skinned New Zealanders (Scragg & Bartley, 2007). Serum vitamin D concentrations are also lower (and decline with age) in women than men (Rockell *et al*, 2006). Recent New Zealand research has demonstrated that vitamin D insufficiency is more common in older, frailer women (Bolland *et al*, 2010).

Muscle weakness is a major cause of falls, and improving muscle strength is important to prevent older people falling. Vitamin D deficiency is associated with poor leg muscle strength and a positive correlation between muscle strength and serum vitamin D levels has been shown. There is some suggestion that serum vitamin D concentrations need to be maintained above 50 nmol/L for benefit in terms of muscle strength (Inderjeeth *et al*, 2007).

Available evidence also supports the logic that increasing serum vitamin D levels via supplementation reduces the risk of falls. Maintaining a serum vitamin D concentration at or above 60 nmol/L has been associated with a 23% reduction in falls and that a concentration of 60 nmol/L is required for fall prevention (Bischoff-Ferrari *et al*, 2009a).

Lower serum vitamin D levels have also been shown to be associated with a significantly greater risk of future admission to a nursing home. Moreover, the risk of admission to a nursing home is proportional to the level of vitamin D deficiency; those people classified as being vitamin D deficient being 2.9-3.8 times more likely, those people classified as being vitamin D insufficient being 2.5-3.0 times more likely, while those people classified as being on the borderline of vitamin D insufficiency being 1.8-2.0 times more likely to be admitted to a nursing home. In this study, lower vitamin D levels were also associated with higher mortality in older people, although the statistical significance of this was lost after adjustment for frailty (Visser *et al*, 2006).

7. Consumer convenience

In the Nutrient Reference Values (NRV) for Australia and New Zealand monograph for vitamin D (2006) it is reported that, with current food supplies and patterns of eating, it is almost impossible to obtain sufficient vitamin D from the diet alone. Unless oily fish is eaten frequently, it is very difficult to attain daily vitamin D intake sufficient for preventing vitamin D insufficiency through dietary sources. Sensible exposure to ultraviolet B radiation is another source of vitamin D, but the opportunity for exposure to sunlight differs throughout the year and care must be taken to avoid an increased risk of skin cancer (Holick, 2007).

Thus, supplementation is appropriate for many people in order to attain levels of vitamin D protective of falls and fracture (Holick, 2007). Down-scheduling the vitamin D classification could improve access to vitamin D by making it easier for those needing high dose supplementation to obtain it without first getting a prescription.

However, any “increase” in consumer convenience does need to be balanced against the fact that high dose vitamin D is indicated for use in the treatment of deficiency states. The data sheet of the one high dose product (Cal.D.Forte®) currently approved in New Zealand links dosage instructions to a patient’s serum 25-OHD concentration:

- For serum 25-OHD of less than 10 µg/L (defined as moderate/severe insufficiency), one 1.25 mg colecalciferol tablet a day for 10 days (loading) then one tablet a month (maintenance)

- For serum 25-OHD of 10 µg/L or higher (defined as mild/moderate insufficiency), one 1.25 mg colecalciferol tablet a month.

These serum levels are in line with a position statement from the Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia (ANZBMS *et al*, 2005). This position statement defines mild vitamin D deficiency as serum 25-OHD levels in the range of 25-50 nmol/L (10-20 µg/L), moderate deficiency in the range of 12.5-25 nmol/L (5-10 µg/L) and severe deficiency at less than 12.5 nmol/L (5 µg/L).

The Cal.D.Forte® data sheet also indicates that, before vitamin D therapy is begun, elevated serum phosphate concentrations must be controlled. Other monitoring recommendations during treatment are also listed, most of them relying on blood tests.

Martindale (2011) provides similar advice, stating that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals (especially initially or if symptoms suggest toxicity) and that plasma phosphate concentrations should be controlled to reduce the risk of ectopic calcification.

Thus, medical intervention, in the form of blood tests, is recommended both at the beginning and throughout treatment. This raises the question of whether pharmacies would have the necessary tools/support for diagnosing vitamin D deficiency and for the on-going monitoring of the patient.

It was because of this issue that the NDPSC in Australia deemed that vitamin D deficiency cannot be diagnosed and managed in a pharmacy setting. Therefore, they decided against a request to down-schedule vitamin D from prescription to pharmacist-only when for internal use in preparations containing more than 25 µg but not more than 125 µg of vitamin D per recommended daily dose.

8. Therapeutic index

Vitamin D has a wide margin of safety, and intoxication (intentional or unintentional) is extremely rare.

The current Nutrient Reference Values (NRV) for Australia and New Zealand sets a safe upper level (UL)[1] of intake for vitamin D of 80 µg (3200 IU) per day in adults aged 19 years and over (NRV, 2006). The UL for adults is based on studies assessing the effect of vitamin D on serum calcium in humans. These studies are briefly summarised in the NRV monograph for vitamin D as follows:

> *Johnson et al (1980) and Honkanen et al (1990) conducted studies with supplementation at 50 µg/day or 45 µg/day for several months and saw no adverse effects. Narang et al (1984), using dosages of 60 µg and 95 µg/day over several months in a non-randomised trial that included 30 normal controls, saw increases above 2.75 mmol/L in serum calcium levels a level considered as defining hypercalcaemia, at 95 µg/day but not at 60 µg/day. However, a well-designed randomised controlled trial by Vieth et al (2001) saw no adverse effect of dosages of 25 µg/day or 100 µg/day over six months in 30 subjects. This finding was confirmed in a later randomised study (Vieth et al 2004) of inpatients with subclinical or marginal deficiency. Vieth et al (2001) felt that the earlier data of Narang et al (1984) may have been erroneous in dosage, citing concerns about lack of independent confirmation of the actual amount of vitamin D administered (there were no measures of serum 25-OHD). There is also some animal evidence of oral vitamin D*

[1] The Upper Level of Intake is defined as the highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the upper level, the potential risk of adverse effects increases.

> *causing non-calcified atherosclerosis of large arteries (Taura et al 1979, Toda et al 1985), suggesting that a cautious approach should be taken to high dose vitamin D in people other than the elderly. Taking all of this into account, the figure of 100 µg/day from Vieth's studies was adopted as the NOAEL[2] and an UF[3] of 1.2 was applied because of the inconsistencies in the studies and they were performed on relatively small number of subjects with pre-existing marginal vitamin D status.*

Higher ULs have been recommended by other researchers. For example, Hathcock *et al* (2007) suggested a UL of 250 µg (10,000 IU) per day based on their review of human clinical trials of vitamin D.

More recently, the United States' Institute of Medicine (IOM) revised its nutrient reference values and UL for vitamin D (IOM, 2011). This was based on more information and higher quality studies than were available when the values were set in 1997. The UL set by the IOM for vitamin D is now 100 µg (4000 IU) per day from age 13 years and over, including during pregnancy and lactation.

Chronic dosing of 1.25 mg colecalciferol per month, as currently occurs with Cal.D.Forte, equates to 40.3-41.7 µg of colecalciferol per day (for a month containing 30-31 days). Even based on the most conservative UL of 80 µg per day, a margin of safety of approximately two can be estimated. In individuals with vitamin D deficiency, the margin of safety will be larger.

9. Toxicity

Ingestion of excessive doses of vitamin D, either as an acute overdose or over prolonged periods, can result in severe toxicity.

Chronic vitamin D-induced hypercalcemia may result in generalised vascular calcification, nephrocalcinosis, and other soft tissue calcification that may lead to hypertension and renal failure. These effects are more likely to occur when the hypercalcemia is accompanied by hyperphosphatemia (Cal.D.Forte data sheet).

Hypercalcemia manifests as anorexia, nausea, polyuria, constipation, weakness, weight loss, headache, depression, vague aches, stiffness, soft tissue calcification, nephrocalcinosis, hypertension, and/or anaemia. In severe cases, hypercalcemia may lead to irreversible heart and renal failure, coma, or death (ANZBMS *et al*, 2005).

Martindale (2011) states that vitamin D is the most likely of all vitamins to cause overt toxicity. It also states that doses of 1.5 mg (60 000 IU) daily can cause hypercalcemia, with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.

The data sheet for Cal.D.Forte® lists the following as early symptoms of vitamin D toxicity associated with hypercalcemia:

- Constipation – usually more frequent in children and adolescents; diarrhoea; dryness of mouth; headache, continuing; increased thirst; increase in frequency of urination, especially at night, or in amount of urine; loss of appetite; metallic taste; nausea or vomiting – usually more frequent in children and adolescents; unusual tiredness or weakness.

[2] No Observed Adverse Effect Level
[3] Uncertainty Factor

Late symptoms of vitamin D toxicity associated with hypercalcemia as described in the data sheet are:

- Bone pain; cloudy urine; high blood pressure; increased sensitivity of eyes to light or irritation of eyes; irregular heartbeat; itching of skin; lethargy (drowsiness); muscle pain; nausea or vomiting and pancreatitis (stomach pain, severe); psychosis, overt (mood or mental changes); - rare; weight loss.

The data sheet states that the dosage necessary to cause toxicity varies with individual sensitivity but, in individuals without malabsorption problems, 250 µg (10,000 IU) a day for more than several weeks or months is the maximum dose. This is in line with a comment by the IOM (2011) that doses above 250 µg per day are known to cause kidney and tissue damage.

10. Adverse reactions

To 31 September 2011, the Centre for Adverse Reactions Monitoring (CARM) had eight reports of suspected adverse reactions in which colecalciferol was listed as a suspect medicine. Reported reactions assessed by CARM as causally related (i.e. possible, probable or certain) were: face oedema, oedema genital, pruritus, skin dry, nail disorder, rash erythematous, prothrombin decreased, drug interaction, rash purpuric, choking, and dysphagia. The decreased prothrombin was assessed as severe and as a possible interaction with warfarin and calcium carbonate.

A recent Cochrane review (Bjelakovic *et al*, 2011) found evidence of renal stone formation when colecalciferol was taken in combination with calcium. Participants in these studies were given vitamin D doses equating to only 7.5-35.7µg (300-1429 IU) per day and calcium doses of 500-1600 mg per day for a median of two years.

11. Abuse potential

There is no evidence in the scientific literature to suggest that vitamin D is a substance of abuse or has any potential for abuse.

12. Inappropriate use

The one high dose vitamin D product currently approved for distribution in New Zealand for the treatment of vitamin D deficiency states contains 1.25 mg (50,000 IU) of colecalciferol per tablet. The maintenance dose is one tablet per month. The potential exists for mistaken administration, where the patient ingests the tablets on a daily basis or takes more than one tablet at a time. There is sufficient risk of toxicity with these scenarios to justify the requirement for a healthcare professional to be involved in the provision of colecalciferol tablets.

A pharmacist would be just as capable of advising on the dosage instructions as a doctor. However, the risk of a patient still misunderstanding does exist, particularly in view of the fact that most of the patient's other medicine would be taken on a daily basis. If the product were a prescription medicine, the risk of a patient still misunderstanding the instructions would be minimised by the doctor enquiring about the need for another prescription so soon. If the product were a restricted medicine, this "safety net" wouldn't exist. A patient could go to a different pharmacist for their next pack and never be questioned about the rapid use. The chances of this continuing to occur are likely to be low given that each new pharmacist would be expected to give the same advice on dosing instructions as the previous pharmacists. Nevertheless the risk does exist. Therefore, special emphasis on the dosing regime at the time of sale would certainly be required if a monthly dose were down-

scheduled. Perhaps linking the down-scheduling to a limit on pack size would also be appropriate (e.g. to a three tablet pack if tablets were to be taken once a month).

The risk of confusion over daily versus monthly dosing was also noted in the Chel *et al* (2007) study, which compared the efficacy of vitamin D supplementation when given daily, weekly and monthly. The trial was conducted in nursing homes and a survey among the nursing staff indicated showed a distinct preference (72%) for daily administration versus weekly or monthly administration. Furthermore, 39% of nursing staff reported the impression that fewer mistakes were made with the daily regimen.

The above considerations raise the question of whether down-scheduling based on a daily dose would be more appropriate. With regards to a suitable daily dose, 40.3-41.7 µg per day is proportional to the once a month intake of 1.25 mg of colecalciferol. However, a daily dose of vitamin D would still not resolve the issue of diagnosing the deficiency in the first place and of the continued monitoring as recommended in Martindale (2011) and the Cal.D.Forte data sheet. It is also noted that no vitamin D-only products are currently approved as medicines at (or below) this strength.

13. Precautions

Martindale (2011) states that vitamin D should not be given to patients with hypercalcemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcemia occurred.

As noted previously, Martindale (2011) also advises that plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification and that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity. Similar monitoring is recommended in infants if they are breast-fed by mothers receiving pharmacological doses of vitamin D.

The data sheet for Cal.D.Forte® lists the following contraindications:

- Colecalciferol is contraindicated in patients with hypersensitivity to any component of this product.
- Except under special circumstances, this medication should not be used when the following medical problems exist:
    - Hypercalcemia
    - Hypervitaminosis D
    - Renal osteodystrophy with hyperphosphatemia (risk of metastatic calcification; however, vitamin D therapy can begin once serum phosphate levels have stabilised).
- Risk-benefit should be considered when the following medical problems exist:
    - Arteriosclerosis or cardiac function impairment (conditions may be exacerbated due to possibility of hypercalcemia and elevated serum cholesterol concentrations).
    - Hypersensitivity to effects of vitamin D (may be involved in causing idiopathic hypercalcemia in infants).
    - Renal function impairment (toxicity may occur in patients receiving vitamin D for nonrenal problems, although toxicity is also possible during treatment of renal osteodystrophy because of increased requirements and decreased renal function).

  - Sarcoidosis, and possibly other granulomatous diseases (increased sensitivity to effects of vitamin D).

Warnings and Precautions listed in the data sheet include:

- Use in pregnancy. Maternal hypercalcemia during pregnancy in humans may be associated with increased sensitivity to effects of vitamin D, suppression of parathyroid function, or a syndrome of peculiar (elfin) faces, mental retardation and congenital aortic stenosis in infants
- Vitamin D should not be administered to patients with hypercalcemia
- Use with care in patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcemia occurred.

Adverse effects listed in the data sheet include:

- Chronic vitamin D-induced hypercalcemia
- Growth arrest in children (especially after prolonged administration of 45µg (1800 IU) of colecalciferol per day).
- Death (as a result of renal or cardiovascular failure caused by vitamin D toxicity).

Interactions listed in the Cal.D.Forte® data sheet include:

- Increased risk of hypercalcemia if co-administered with thiazide diuretics and calcium.
- Vitamin D requirements may be increased by some antiepileptics (e.g. carbamazepine, phenobarbitone, phenytoin, and primidone), barbiturates, cholestyramine, colestipol, hydantoin anticonvulsants, mineral oil, and primidone.

These types of warnings and precautions would all need to be included on the labelling or a package insert if the classification of vitamin D was to be down-scheduled to a restricted medicine.

14. Communal harm

The risk of harm is predominantly to individuals, as discussed in the previous sections of this report. Wider use of vitamin D in adults deficient in vitamin D or at risk of deficiency is unlikely to result in harm to the community, rather the resultant reduction in falls could result in health and societal benefits.

15. Risk assessment

The research suggests some role for vitamin D in the prevention of falls and fractures. Given the prevalence of vitamin D deficiency, particularly in older individuals, there appears to be a need for high dose vitamin D products. This need is evidenced by the large number of patients using the Pharmac-subsidised vitamin D drug Cal.D.Forte. However, need does not necessarily mean that the classification of an ingredient should change.

The safety of the ingredient is an important consideration. Vitamin D can generally be considered safe, with a UL ranging between 80-250 µg depending on the research group. With regards to a 1.25 mg dose taken monthly, this equates to a daily dose of 40.3-41.7 µg. Even based on the more conservative UL of 80 µg, this gives a safety margin of approximately two. When a 1.25 mg vitamin D tablet is used as intended (for individuals with vitamin D deficiency states), the safety margin would be higher.

Nevertheless, vitamin D use is associated with risks, some of which can be particularly serious. The risks of adverse effects and/or the seriousness of those effects increases when individuals have certain medical conditions (e.g. heart disease, renal impairment, hypercalcemia, hyperphosphataemia) or are taking certain medications or supplements

(e.g. thiazide diuretics, calcium). The appropriateness of the medication for an individual therefore needs to be assessed against their medical history and blood tests. While pharmacists are certainly capable of enquiring about other medications used by a patient and the patient's medical history (especially if given suitable training regarding what risk factors to enquire about), it is not clear how pharmacists would monitor calcium or phosphate levels or other blood parameters in the absence of a blood test (something generally organised by a doctor).

Likewise, the Cal.D.Forte data sheet links dosage to the severity of the vitamin D deficiency. Deficiency is defined by serum 25-OHD levels which, once again, require a blood test to determine. The data sheet also recommends monitoring patients during treatment, generally via results from blood tests.

The other risk factor to consider is patient confusion over daily versus monthly administration. This risk could be minimised by specific emphasis on dosage instructions at the point of sale by the pharmacist or by linking down-scheduling to a daily dose only or a limited pack size.

With regards to a suitable daily dose, a quantity of 40.3-41.7 µg would be proportional to the once a month intake of 1.25 mg colecalciferol. It is also within the NRV's UL of 80 µg per day and within the more recent UL of 100 µg per day suggested by the IOM. For scheduling purposes, the daily quantity could be rounded up to 45 µg.

Increasing the adult daily dose to the 80 µg or 100 µg UL is also a possibility. However, it should be noted that no products are currently registered in New Zealand for this daily dose. The IOM has also stressed that the UL should not be misunderstood as amounts people need or should strive to consume, and this must be particularly so on a long term basis. Even levels below the UL can be associated with adverse effects under certain circumstances, as illustrated in Bjelakovic's meta-analysis of long-term use of quantities equating to a daily dose of 7.5-35.7µg (300-1429 IU) vitamin D in the presence of calcium supplementation.

16. Matters for consideration by the MCC

The following matters should be considered by the MCC when determining whether it is appropriate to reclassify vitamin D from prescription medicine to restricted medicine for the prevention and treatment of vitamin D deficiency states in adults:

- Whether a pharmacist would have the necessary tools/support for diagnosing vitamin D deficiency in adults and for on-going monitoring of the patient.
- Whether pharmacists would require training if down-scheduling was to occur.
- Whether the down-scheduling to restricted medicine should include doses taken monthly (up to 1.25 mg) or be restricted to those taken daily (e.g. up to 45 µg).
- Whether the down-scheduling should be linked to a limit on pack size (e.g. to a supply of three months).
- What warnings and precautions would need to be displayed on the labels (with any other warnings to appear in the package insert).

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18. Appendices

1. ACC Claims Data for Falls 2005-2007 (from Robertson & Campbell, 2008
2. Injury Prevention Research Unit (IPRU) – National Injury Query System (NIQS)
   - Falls by Age
   - Falls by Year
   - Falls by Location
3. Cal.D.Forte data sheet
4. Extract from the minutes of the 57th meeting of the Australian National Drugs and Poisons Schedule Committee (NDPSC)