

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 14

September 2012

VITAMIN D DEFICIENCY IN AT-RISK GROUPS: PART 2 TREATMENT

Key Points

- PACEF do not recommend the *prescribing* of vitamin D supplements for the *prevention of vitamin D deficiency* in those at risk. Eligible patients should be signposted to the *Healthy Start* scheme; all others should be advised either to purchase *Healthy Start* products from participating outlets or alternative vitamin D supplements from their local community pharmacy or healthfood store. Existing guidance around the prescribing of calcium and vitamin D for the prevention of hip fracture, non-vertebral fracture and falls remains unchanged (see *PACE Bulletin* Vol 6, No 6 (May 2012)).
- PACEF fully support the prescribing of vitamin D supplements in patients with a diagnosed severe deficiency of vitamin D or those with a deficiency associated with disease risk (i.e. all those with a 25 hydroxyvitamin D level of less than 50 nmol/litre) (see treatment guidelines below). Prescribing of vitamin D should be reserved for the treatment of proven vitamin D deficiency with associated symptoms.
- Colecalciferol 20,000IU capsules (Dekristol) (60,000IU weekly (3 capsules) weekly for 12 weeks) are recommended first line for the treatment of severe vitamin D deficiency (<25 nmol/l 25 hydroxyvitamin D). Colecalciferol (Dekristol) 20,000IU capsules are designated GREEN for this indication.
- Colecalciferol 800IU capsules (Fultium D3) one to two capsules (800IU-1600IU) daily are recommended first line for the treatment of deficiency (25 hydroxyvitamin D level 25 to 50 nmol/l). Colecalciferol 800IU capsules (Fultium D3) are designated GREEN for this indication.
- Other second and third line options are also defined with selection informed by the MHRA *Hierarchy of risk on the basis of product origin* (see below). Unlicensed specials should be used as a last resort or where there is a genuine patient need for a particular type of formulation.
- Prescribers are urged to be specific about the product required on the prescription and to discuss product availability with their dispensary staff or their local community pharmacist or their local PCT prescribing adviser prior to prescribing. Further information on available products is provided in Appendix 2 (see below).
- Where vitamin D deficiency emerges as a recurrent problem for an individual, PACEF are in support of maintenance therapy on NHS prescription. Where prescribed maintenance therapy is indicated, colecalciferol 800IU capsules (Fultium D3) one to two capsules (800 IU-1600 IU) daily should be used.

Introduction

A recent nationwide survey in the United Kingdom showed that more than 50% of the adult population have insufficient levels of vitamin D and that 16% have severe deficiency during winter and spring (*BMJ* 2010;340:bmj.b5664). In Part 1 of this two part *PACE Bulletin* special we provided advice on the prevention of vitamin D

deficiency in at risk groups (see *PACE Bulletin* Volume 6 No 6 (May 2012)). In Part 2 we provide detailed guidance on the management of confirmed vitamin D deficiency.

Who is at risk of vitamin D deficiency?

- All pregnant and breastfeeding women, especially teenagers and young women.
- Infants and young children under 5 years of age.
- Older people aged 65 years and over.
- People who have low or no exposure to the sun (e.g. those who cover their skin for cultural reasons; the housebound or those confined indoors for long periods).
- People who have darker skin (e.g. people of African, African-Caribbean and South Asian origin) whose bodies cannot make as much vitamin D.
- People who suffer from medical conditions that alter how the body handles vitamin D (e.g. pancreatic insufficiency, inflammatory bowel disease, Crohn's disease, coeliac disease, certain liver and kidney diseases, post bariatric surgery or post gastrectomy).
- People taking certain medicines (e.g. carbamazepine, cholestyramine, glucocorticoids, orlistat, phenytoin, primidone, rifampicin, barbiturates, some anti-HIV medicines and transplant medicines).
- People who are obese (vitamin D is sequestered in body fat).
- People with severe liver failure, nephrotic syndrome or chronic kidney disease.

Health care professionals need to ensure that those identified as being at risk get enough vitamin D either by increasing their exposure to sunlight, increasing dietary intake of vitamin D or informing them how they can access vitamin D supplements.

PACEF Recommendation:

PACEF do not recommend the *prescribing* of vitamin D supplements for the *prevention of vitamin D deficiency* in those at risk. Eligible patients should be signposted to the *Healthy Start* scheme; all others should be advised either to purchase *Healthy Start* products from participating outlets or alternative vitamin D supplements from their local community pharmacy or healthfood store. Existing guidance around the prescribing of calcium and vitamin D for the prevention of hip fracture, non-vertebral fracture and falls remains unchanged. See *PACE Bulletin* Volume 6 No 6 (May 2012) for more detail.

What are the symptoms suggestive of vitamin D deficiency in adults?

- General vague aches and pains are the most common presenting symptoms.
- In more severe deficiency, there may be more severe pain and also weakness that may lead to difficulty standing up or climbing stairs.
- Bone pains may develop and are typically felt in the ribs, hips, pelvis, thighs and feet.
- Proximal muscle weakness may occur (i.e. in the quadriceps and glutei). This may cause difficulty rising from a chair and /or a waddling gait.
- More diffuse muscular aches and muscle weakness, including in the limbs and back, are also common and may be labelled as "fibromyalgia" or as a somatisation of depression (*BMJ* 2008; 336: 1371-4).
- Fractures typically femoral neck, scapula, pubic rami, ribs and vertebrae.
- Swelling, tenderness and redness at pseudo-fracture sites.
- Carpopedal spasm, tetany, seizures or irritability due to hypocalcaemia (requiring urgent treatment).

It is important to exclude other potential causes for the above symptoms such as myeloma, rheumatoid arthritis, polymyalgia and hypothyroidism. Patients presenting

with a fracture will need to be assessed for the possibility of osteoporosis and treated in accordance with NICE and local guidance. While such patients would normally be started on an evidence based combination of calcium and vitamin D, an identified vitamin D deficiency based on 25-hydroxyvitamin D levels may necessitate the prescribing of a higher dose of vitamin D in accordance with doses recommended below.

When is further investigation necessary?

Population screening by measuring vitamin D levels is unnecessary even in high risk populations. Investigations to determine the presence of vitamin D deficiency should **only** be carried out if the patient presents with one or more of the symptoms of vitamin D deficiency and falls within one or more of the at risk categories listed above.

What investigations need to be done?

The most reliable way to determine vitamin D deficiency is to assay the serum levels of 25-hydroxyvitamin D. If vitamin D deficiency is suspected, the following biochemical tests should be requested:

- 25 – hydroxyvitamin D
- Bone profile
- Parathyroid hormone (PTH) - to exclude primary hyperparathyroidism.
- Liver function tests (LFTs) - to exclude hepatic failure.
- Urea and electrolytes (U&E's) - to exclude renal failure.
- Full Blood Count (FBC) - anaemia may be present if there is malabsorption.

Specialist referral will be necessary in patients with:

- Liver disease.
- Renal disease, including the presence of renal stones.
- Hypercalcaemia
- Metastatic cancer.
- Lymphoma.
- Sarcoidosis.
- Tuberculosis.
- Skeletal deformity.
- Short stature.
- Focal bone pain.
- Suspicion of malabsorption

How is vitamin D deficiency defined?

Definitions

Vitamin D deficiency is normally defined as a concentration of 25 hydroxyvitamin D of less than 25nmol/litre. This is the level below which parathyroid hormone (PTH) starts to rise causing increased bone turnover and hence the symptoms associated with osteomalacia (these include rickets in children and osteoporosis and fractures in adults). Vitamin D is seasonal, but replete levels should be > 75 nmol/L. The table below identifies different levels of deficiency according to 25 hydroxyvitamin D levels and recommends a range of different approaches to treatment dependent upon the level of deficiency (i.e. severe deficiency, deficiency associated with disease risk, insufficiency and replete).

Level of deficiency	25 hydroxyvitamin D level	Recommended treatment
Severe deficiency (associated with osteomalacia including rickets in children and osteoporosis and fractures in adults)	<25 nmol/l 25 hydroxyvitamin D	Prescribe 60,000 units weekly of colecalciferol for 12 weeks (either as a single weekly dose or 20,000 units three times a week).
Deficiency associated with disease risk	25-50 nmol/l 25 hydroxyvitamin D	Prescribe 800-1600 units of colecalciferol daily for 12 weeks
Insufficiency	50-75nmol/l 25 hydroxyvitamin D	Consider lifestyle advice including: increased dietary intake and safe sun exposure. Refer to PACEF guidance on the prevention of vitamin D insufficiency
Replete	>75nmol/l 25 hydroxyvitamin D	No treatment necessary

Note: The immunoassay used in the Path Links laboratories does not detect D2 (ergocalciferol) or D3 (colecalciferol), instead it measures the 25 hydroxylated metabolite.

PACEF Recommendation:

PACEF fully support the prescribing of vitamin D supplements in patients with a diagnosed severe deficiency of vitamin D or those with a deficiency associated with disease risk (i.e. all those with a 25 hydroxyvitamin D level less than 50 nmol/litre).

How is vitamin D deficiency treated?

Colecalciferol (vitamin D3) is considered the preferred form of vitamin D for treatment as it raises vitamin D levels more effectively than ergocalciferol (vitamin D2) and has a longer duration of action. The majority of colecalciferol containing products do not have a marketing authorisation; they are available either as food supplements or unlicensed specials and can be costly. Dependent upon the dosage required, the preferred colecalciferol products in Lincolnshire are colecalciferol (Dekristol) 20,000 IU capsules (unlicensed but preferred for the treatment of severe deficiency) and colecalciferol 800IU capsules (Fultium D3) (licensed for the treatment of deficiency but does not contain a sufficiently high dose of colecalciferol to treat severe deficiency). Unlicensed liquid specials of vitamin D should not be routinely prescribed due to their high cost; use of these products should be reserved for those patients who are unable to use either colecalciferol capsules or the injectable formulations. PACEF have recently published updated guidance on the use of specials (see *PACE Bulletin*, Volume 6 No 11 (September 2012)).

Treatment of severe deficiency (25 hydroxyvitamin D level less than 25nmol/l)

- **Preferred first option:** colecalciferol (Dekristol) 20,000 unit capsules. The required dose is 60,000 units weekly which can be prescribed as a single weekly dose or 20,000 units three times a week. This product does not have a marketing

authorisation in the UK but is a licensed medicine in Germany; it is preferred to other high dose colecalciferol products which are classed as food supplements or unlicensed specials.

- **Alternative option** : Consider giving 300,000 units of IM ergocalciferol in two injections 3 months apart. This option may be appropriate for those patients who are unable to comply with an oral dosage regimen or if there are concerns about malabsorption. Ergocalciferol injection 300,000 units per ml is a licensed product and should be used where possible. Where availability is a problem, colecalciferol injection 300,000 units per ml presents an unlicensed, but suitable alternative (see Appendix A).
- **Alternative option**: If capsules or injection are not suitable, consider using an oral liquid. Liquid products are costly and often have a short shelf life and should be reserved for those individuals for whom there is no alternative treatment. Where a liquid formulation is required, first choice should be Zymad colecalciferol drops 10,000 units/ml; this Novartis product does not have a UK marketing authorisation, but is licensed and manufactured in France.

Treatment of deficiency (25 hydroxyvitamin D level 25 to 50 nmol/l)

A treatment course of doses in the range of 800 units to 1600 units of colecalciferol should be taken daily for 12 weeks.

- **Preferred first option**: Colecalciferol 800 unit capsules (Fultium D3) one – two capsules (800 IU-1600 IU) daily. This product has a UK marketing authorisation and is licensed for the prevention and treatment of vitamin D deficiency.
- **Alternative option**: Fultium D3 capsules contain arachis oil and are not suitable for those with a peanut or soya allergy. A suitable alternative would be Solgar Vitamin D3 colecalciferol capsules available in 400 IU, 660 IU or 1000 IU strengths. These are not licensed medical products and are classed as a food supplements; they are not listed in Part XVIII A of the Drug Tariff (the black list) and can be prescribed on NHS prescription.
- **Alternative option**: Ergocalciferol injection 300,000 units per ml in a single dose by intramuscular injection once or twice a year. Ergocalciferol 300,000 IU is the licensed product and should be used if possible; availability can be a problem so a suitable alternative is an unlicensed product - colecalciferol injection 300,000 units per ml.

Maintenance treatment

Maintenance therapy at a dose of 800 to 1600 units of colecalciferol daily may be required once deficiency has been corrected for those patients who were severely deficient and are still considered to be at risk. In some cases there may be a requirement for lifelong therapy if the risk factors for the condition cannot be resolved. Options for the provision of maintenance treatment are:

- Prescribe colecalciferol 800 unit capsules (Fultium D3) one – two capsules (800 IU-1600 IU) daily. This product is only available on prescription and should be reserved for maintenance treatment at the discretion of the responsible clinician. Factors to be taken into account before deciding to continue to prescribe vitamin D supplements will include the underlying cause of the deficiency and the ability and willingness of the patient to adopt the necessary life style changes including increasing their exposure to sunlight and ensuring adequate dietary intake of vitamin D.
- or**
- Encourage the patient to make lifestyle changes such as increasing dietary intake of vitamin D, increasing safe sun exposure and increasing vitamin D

intake with supplements as outlined in the *PACE Bulletin* on the prevention of Vitamin D insufficiency. For patients not exempt from prescription charges these supplements often are less expensive to purchase OTC than to obtain on prescription

PACEF Recommendation:

Where vitamin D deficiency emerges as a recurrent problem for an individual, PACEF are in support of continuing prescribing of vitamin D maintenance therapy on NHS prescription. Where prescribed maintenance therapy is indicated, colecalciferol 800 IU capsules (Fultium D3) one to two capsules (800 IU – 1600 IU) daily should be used. The 30 day treatment cost is between £3.60 and £7.20.

What are the cautions and contraindications to vitamin D therapy?

Vitamin D supplements should be used with caution in those with primary hyperparathyroidism, renal stones and severe hypercalciuria. Vitamin D is contraindicated in patients with hypercalcaemia or metastatic calcification.

What monitoring is required and when is specialist referral necessary?

Measure 25-hydroxyvitamin D, Parathyroid Hormone (PTH) and calcium after 3 months. Aim for 25-hydroxyvitamin D 'replete' level, with calcium and PTH levels within reference ranges. If normal at 3 months there is no need to repeat the tests. If vitamin D levels are not normal but improving after 3 months, consider repeating tests in a further 3 to 6 months dependent on the patients overall clinical condition.

If 25-hydroxyvitamin D levels are not improving after 3 months, refer to a consultant endocrinologist. Further tests will need to be conducted at a three and six months.

If the PTH level remains elevated whilst vitamin D levels are normal, refer to a consultant endocrinologist.

If the patient develops hypercalcaemia, refer to a consultant endocrinologist.

If vitamin D levels are improving but are not yet replete, consider options for maintenance treatment.

Further Product Information

Colecalciferol 800IU capsules (Fultium D3)

Fultium D3 is a newly launched licensed formulation of colecalciferol (vitamin D3). It is licensed for the treatment of deficiency of vitamin D, but does not contain sufficient colecalciferol to effectively treat severe deficiency. The licensed dose is between 800IU to 3200IU daily to treat deficiency of vitamin D. Lincolnshire guidance recommends Fultium D3 at a dose of 800IU to 1600IU (one to two capsules) daily as the preferred first line option in the treatment of deficiency of vitamin D (see above). Colecalciferol 800IU capsules (Fultium D3) are designated GREEN for this indication. Fultium D3 capsules contain arachis oil and are unsuitable for those with a peanut or soya allergy.

Colecalciferol 20,000 IU capsules (Dekristol)

Colecalciferol 20,000 IU capsules (Dekristol) contain a significantly higher concentration of colecalciferol (20,000IU) and are normally prescribed at a dose of 60,000IU (3 capsules) weekly for 12 weeks to treat severe vitamin deficiency. Dekristol capsules do not have a marketing authorisation in the UK, but do have a marketing authorisation in Germany. In the absence of a licensed product in the UK, a product that is licensed abroad becomes the next preference in accordance with the MHRA *Hierarchy of risk on the basis of product origin* (see Appendix 1).

Further information on the range of vitamin D preparations available in the UK is tabulated below (see Appendix 2). Prescribers are urged to be specific about the product required on the prescription and to discuss product availability with their dispensary staff or their local community pharmacist or their local PCT prescribing adviser prior to prescribing. The information provided in this *Bulletin* should ensure appropriate product selection in most instances, although problems with availability may necessitate more creative problem solving. The MHRA hierarchy should be applied to determine appropriate alternatives (see Appendix 1). Unlicensed specials should be used as a last resort or where there is a genuine patient need for a particular type of formulation.

Further information

The full text of the United Lincolnshire Hospitals Trust/NHS Lincolnshire, *Protocol for the diagnosis and management of vitamin D deficiency in adults* is available on the PACEF section of the NHS Lincolnshire website.

Acknowledgements

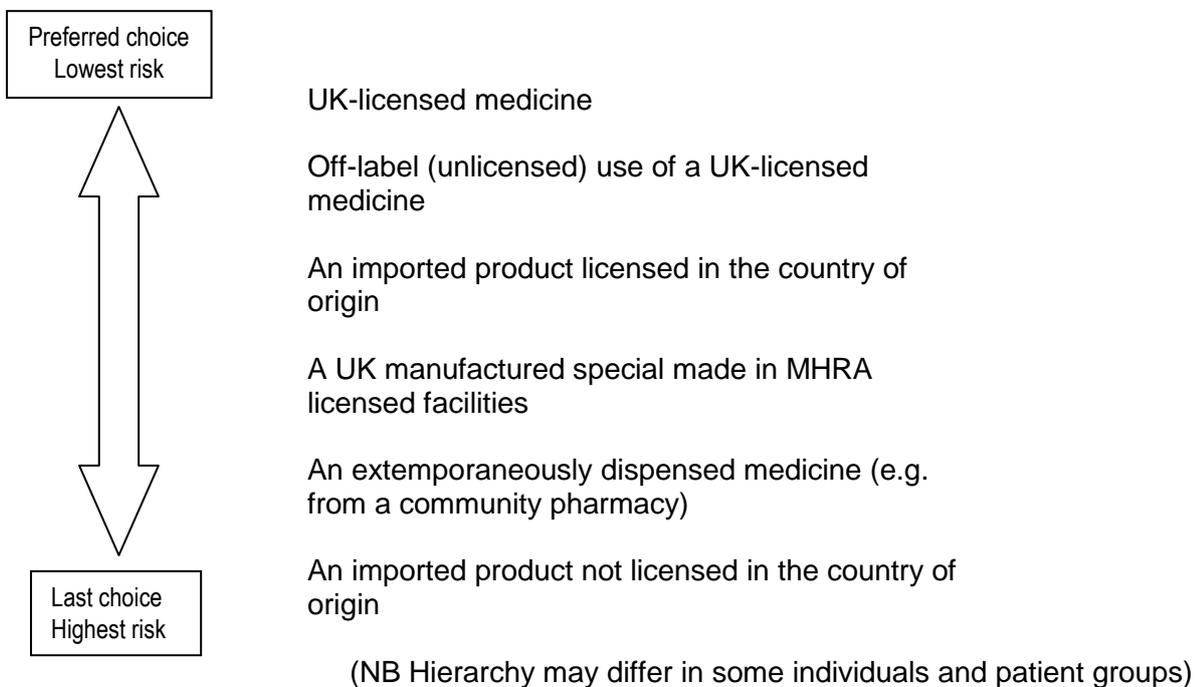
Many thanks to Dr R Sriraman, Consultant Physician and Endocrinologist at ULH, Dr Ravikumar, Consultant Physician and Endocrinologist, ULH, Dr Jagger, Consultant Clinical Biochemist, ULH and Cathy Johnson, Interface Lead Pharmacist, NHS Lincolnshire for their help in the preparation of this *Bulletin*.

References

1. Diagnosis and management of vitamin D deficiency BMJ 2010; 340 doi: 10.1136/bmj.b5664 (Published 11 January 2010) Cite this as: BMJ 2010;340:bmj.b5664
2. Imperial centre for Endocrinology, <http://www.imperialendo.com>
3. Vitamin D Deficiency in Adults. St George's Healthcare NHS trust and Wandsworth NHS. August 2010.
4. Derbyshire Joint Area Prescribing Committee (JAPC) Guidance on the prevention, diagnosis and management of vitamin D deficiency in primary care. May 2012.
5. Leicestershire Medicine Strategy Group. Diagnosis and management of vitamin D deficiency for non-specialists – Interim Guidance.
6. Summary of product characteristics – Fultium D3 800IU capsules, Internis Pharmaceuticals Ltd. Last updated 23rd January 2012.

Appendix 1

Medicines and Healthcare products Regulatory Agency (MHRA): *Hierarchy of risk on basis of product origin* (adapted from MHRA guidance)



Appendix 2

The information in this table is intended to act as a guide to prescribers as to the range, price and availability of licensed and unlicensed colecalciferol preparations. The range and price of available products is subject to frequent change. For the most up to date information please contact either NHS Lincolnshire's Prescribing and Medicines Optimisation Team or any of the United Lincolnshire Hospital Pharmacy Departments.

VITAMIN D CONTAINING PREPARATIONS (FIRST-LINE CHOICES IN BOLD)				
High dose oral formulations				
PRODUCT NAME AND STRENGTH	MANUFACTURER DISTRIBUTORS	Cost (BNF List price or from manufacturer)	LICENSING	SUITABLE FOR VEGETARIANS
Dekristol (colecalciferol) capsules 20 000 IU (50 capsules)	Available from Pharmarama, tel. 0208 238 6770; IDIS world medicines, tel. 01932 824 100; Martindale Pharmaceuticals, tel. 0800 137 627 UL medicines tel no 01923 204 3333	Pharmarama £14.75 IDIS £ 19.30 Martindale £18.45 Mawdsleys £12.00	Does not have UK marketing authorisation. Manufactured and licensed by MIBE Pharmaceuticals, Germany	Contains gelatine so not suitable for vegetarians. Contains groundnut oil, peanut oil so not suitable for those with nut allergy
Vitamin D 3 capsules 20,000 IU (50 caps), 50,000 IU (50 caps) and 100,000 IU (30caps) Available from Encap. 01506 448080	Available from Encap. 01506 448080		Does not have UK marketing authorisation. Manufactured as a special by Encap Drug Delivery	√ Suitable for vegans.
ProD3 colecalciferol Wide range of strengths including 10,000 IU, 20,000 IU and 30,000 IU	Available from AAH Pharmaceutical tel no 024 7643 2000	10,000 IU £14.99 (30) 20,000 IU £19.99 (30) 30,000 IU £24.99 (10)	Does not have UK marketing authorisation. Marketed as a nutritional supplement	Colecalciferol is derived from sheep's wool fat however company has confirmed the product is suitable for vegetarians.
Parenteral products				
Ergocalciferol injection 300 000 IU/mL (10x1mL)	Available from Focus Pharmaceuticals tel. 01283 495 280	£93.50	Product has UK marketing authorisation	√
Vitamin D3 Streuli Colecalciferol injection 300 000 IU/mL (10x1mL)	Available from IDIS world medicines, tel. 01932 824 100	£43.50	Does not have UK marketing authorisation. Manufactured and licensed by Streuli Pharmaceuticals , Switzerland.	Colecalciferol is derived from sheep's wool fat and produced synthetically. May not be suitable for vegetarians.
Colecalciferol injection 300,000 IU/ml	Available from Mawdsleys	£12.68	Does not have UK marketing authorisation. Manufactured and licensed in Switzerland.	Colecalciferol is derived from sheep's wool fat however company has confirmed the product is

				suitable for vegetarians. Contains peanut oil.
Ostelin OS ergocalciferol 400,000 IU/2ml	Available from UL medicines tel no 01923 204 333	£8.80	Does not have UK marketing authorisation. Manufactured and licensed in Italy.	No information available from supplier. Contains peanut oil.
Lower dose oral formulations				
PRODUCT NAME AND STRENGTH	MANUFACTURER DISTRIBUTORS	Cost (BNF List price or from manufacturer)	LICENSING	SUITABLE FOR VEGTARIANS AND VEGANS
Fultium D3 capsules 800IU.	Available via normal wholesaler routes	£3.60 (30)	Product has UK marketing authorisation	Contains gelatine so not suitable for vegetarians. The gelatine is halal and kosher compliant. Contains arachis oil so not suitable for those with peanut allergy.
Solgar Vitamin D3 25µg (1000 IU) softgels (100 capsules)	Available for purchase only from www.solgar.co.uk		Does not have UK marketing authorisation. Marketed as a nutritional supplement	Contains gelatine not suitable for vegetarians.
ProD3 colecalciferol Wide range of strengths including 400IU,1000IU,2500IU	Available from AAH Pharmaceutical tel no 024 7643 2000	£4.99-19.99	Does not have UK marketing authorisation. Marketed as a nutritional supplement	Colecalciferol is derived from sheep's wool fat however company has confirmed the product is suitable for vegetarians.
Vegan vitamin D2 (ergocalciferol) 800IU,2400IU	Available for purchase only. www.devanutrition.com		Does not have UK marketing authorisation. Marketed as a nutritional supplement	√
SunVit D3 colecalciferol 1000IU	Available to purchase only	£8.16 (online) £5.00 (NHS cost)	Does not have UK marketing authorisation. Marketed as a nutritional supplement	Colecalciferol is derived from sheep's wool fat may be unsuitable for vegetarians.

Liquid formulations				
PRODUCT NAME AND STRENGTH	MANUFACTURER DISTRIBUTORS		LICENSING	SUITABLE FOR VEGTARIANS AND VEGANS
Zymad colecalciferol drops 10,000 IU/ml 10 ml 30 day expiry after opening	Available from IDIS tel no 01932 824 100 Mawdsleys tel no 01302 553 000 UL medicines tel no 01923 204 333	IDIS £8.60 Mawdsleys £4.32 UL £6.13	Does not have UK marketing authorisation. Manufactured and licensed by Novartis, France	
Colecalciferol liquid 3000 IU/mL (100 mL or 500 mL bottles) 30 day expiry once opened.	Available from Martindale Pharmaceuticals, tel. 0800 137 627	100ml £80.52 500ml £107.33	Does not have UK marketing authorisation. Manufactured as a special by Martindale	
Colecalciferol liquid 1000 IU/5 mL (30mL–500mL bottle) 30 day expiry once opened	Available from Martindale Pharmaceuticals, tel. 0800 137 627	30ml £106.64 200ml £107.20 500ml £108.14	Does not have UK marketing authorisation. Manufactured as a special by Martindale.	

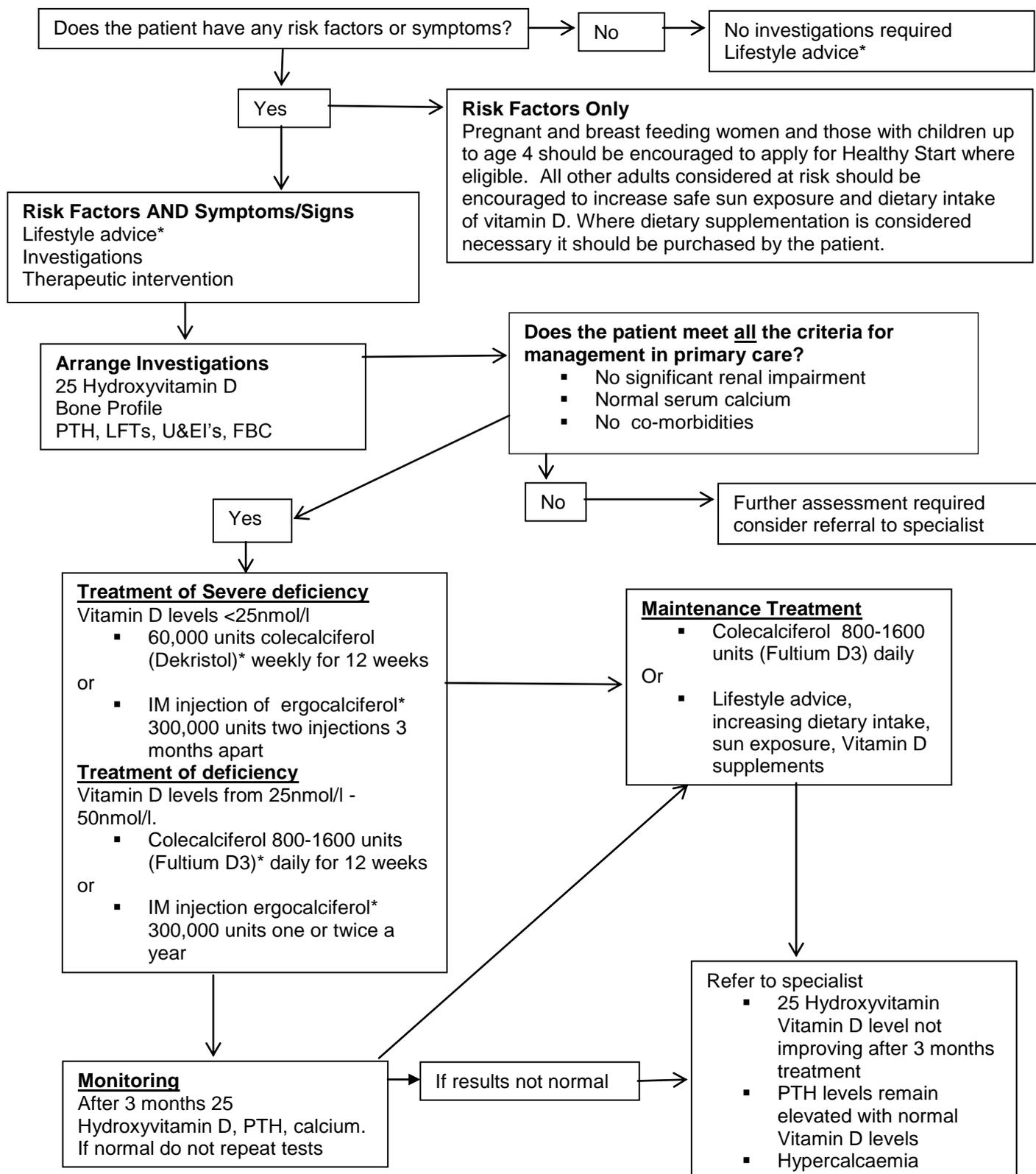
*only manufactured on request

References:

1. East & South East England Specialist Pharmacy Services, Vitamin D deficiency and insufficiency using appropriate available products. June 2011.
2. MIMS April 2012
3. UKMI Medicines Q&A's. Which vitamin D preparations are suitable for a vegetarian or vegan diet? Q&A 387.1 prepared 6th March 2012.

Appendix 3: Diagnosis and Management of Vitamin D Deficiency in Primary Care – Treatment Algorithm

Population screening by measuring Vitamin D levels is unnecessary, even in high risk populations.



*Alternative products may be required if the patient has nut allergies, swallowing difficulties or a vegetarian diet.