

Guidance for the treatment of Vitamin D insufficiency and deficiency

Vitamin D is essential for musculoskeletal health. Vitamin D insufficiency may cause secondary hyperparathyroidism, bone loss, muscle weakness, falls and fragility fractures in the elderly. Vitamin D deficiency can lead to osteomalacia in adults and rickets in children. It has also been suggested that inadequate vitamin D has involvement in disorders of the immune system, cancer and metabolic disorders

Sources of vitamin D:

1. Sunlight – this is the major natural source of vitamin D. White populations require 20-30 mins of midday summer sunlight exposure to the face and forearms 2-3 times a week. Individuals with pigmented skin require 2-10 times the exposure of someone with fair skin.

The UK does not have enough suitable UVB during October to March to generate vitamin D.

2. Diet – There are few foods that are rich in vitamin D, sources include oily fish (200-400 IU/100g) and some breakfast cereals (120-320 IU/100g). Dietary intake of vitamin D is thought to be low (80-160 IU/day) on average.

Who to test:

1. Patients with bone diseases i.e. osteomalacia or osteoporosis or Paget's disease.

It is recommended that vitamin D deficiency is corrected prior to commencing osteoporosis treatment with a potent antiresorptive agent (zoledronate or denosumab), to avoid the development of hypocalcaemia. Routine 25OHD testing may not be required in an osteoporosis patient where the decision has already been made to co-prescribe vitamin D with an antiresorptive agent.

2. Patients with musculoskeletal symptoms – if patients are suspected of having symptoms caused by osteomalacia or have chronic widespread pain, measurement of 25OHD are reasonable.

N.B. Routine 25OHD monitoring is unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption, or where poor compliance with medication is suspected.

Assessment of vitamin D status

Vitamin D status is currently best assessed by measurement of serum 25OHD (25-Hydroxy vitamin D) The National Osteoporosis Society has proposed that the following vitamin D thresholds are adopted:
Serum 25OHD: <30 nmol/L= deficient
30-50nmol/L= adequate in some
>50nmol/L = sufficient for almost the whole population

The main methods for estimating 25OHD are immunoassay or HPLC attached to fluorescence or mass spectrometry (MS) detection (tandem MS).



If re-testing of Vitamin D levels is needed (e.g. if compliance issues or if no improvement in symptoms) the minimum testing interval is 3-6 monthly. Please also note that some laboratories have requesting strategies in place to ensure appropriate requesting therefore clinical details must have relevant information to the vitamin D request.

Who and How to treat:

Key aims for treating vitamin D deficiency in patients with bone disease:

The NOS recommends vitamin D₃ as the vitamin D preparation of choice for the treatment of vitamin D deficiency, an oral preparation should be used where possible

Treatment should be based on fixed-loading doses and maintenance therapy

Adequate doses of Vitamin D should be used to ensure correction of deficiency (ideally >50nmol/L)

The clinical consequences of Vitamin D deficiency should be reversed in a timely manner

Toxicity should be avoided

Where rapid correction of vitamin D deficiency is required e.g. in patients with symptomatic disease or those commencing therapy with a potent antiresorptive agent (zoledronic acid or denosumab) use fixed loading doses followed by a regular maintenance therapy

In less urgent correction of vitamin D deficiency and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the need for loading doses

Treatment with vitamin D in those patients with suspected malabsorption disorder, renal or hepatic disease or any condition where there may be an increased risk of toxicity should be discussed with secondary care

Promote the relevance of adequate dietary calcium intake and encourage the use by patients and practitioners of calcium calculators e.g. Calcium Calculator

Osteoporosis patients who are unable to reliably or regularly consume 700mg of calcium daily should receive supplementation with calcium-only or combined calcium and vitamin D supplements.

Combined calcium and vitamin D preparations should not be used as sources of vitamin D for loading doses due to the resulting high dosing of calcium

Supplements should be taken with food to aid absorption



Vitamin D status	Treatment required	Suggested treatment regime	Monitoring recommendations
Serum 25OHD <30nmol/L (deficiency of vitamin D)	Treatment recommended	An adult loading regime to provide a total of approximately 300,000 IU vitamin D divided into a weekly or daily doses over 6 to 12 weeks depending on product This should be followed by a maintenance regime (See table at end of document for treatment options)	Routine monitoring of serum 25OHD is unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected. Adjusted serum calcium should be checked 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked.
Serum 25OHD 30-50 nmol/L (insufficiency of vitamin D)	Treatment advised when: -Fragility fracture, documented osteoporosis or high fracture risk -treatment with antiresorptive agent for bone disease -symptoms suggestive of vit D deficiency -increased risk of developing vit D deficiency e.g. reduced exposure to sun, religious/cultural dress code, dark skin -raised PTH Medication with antiepileptic drugs or oral glucocorticoids Conditions associated with malabsorption	Where correction of Vitamin D deficiency is less urgent maintenance therapy may be started without the use of loading doses; a daily adult maintenance dose of between 800-2000 IU/day (given daily or intermittently at higher doses) is advised. (See table at end of document for treatment options)	During long-term treatment serum calcium levels should be followed and renal function should be monitored via serum creatinine. Monitoring is particularly important in the elderly who are on concomitant cardiac glycosides or diuretics and in those with a high tendency to calculus formation. Decrease or discontinue treatment when hypercalciuria occurs. Colecalciferol should be used



			with caution in those with impaired renal function (calcium and phosphate levels should be monitored). Colecalciferol should not be used in those with severe renal insufficiency; alternative vitamin D forms should be used.
Serum 250HD >50 nmol/L	No	Provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet	
Adult groups at risk of vitamin D deficiency: <ul style="list-style-type: none">• All pregnant and breastfeeding women, especially teenagers and young women• Older people 65 years+• People with low or no sun exposure e.g. house-bound or who cover their skin for cultural/religious reasons• Those with darker skin e.g. African, South Asian origin as their bodies are unable to make as much vitamin D		Take a daily supplement containing 10µg (400 IU) of vitamin D. Vitamin D supplements can be purchased from Community pharmacies	
All infants/toddlers from 6 months-5 years (unless drinking 500mL or more of infant formula)		Take a daily supplement containing 280 IU/day	
Breastfed babies 1 month – 6 months if mother is vitamin D insufficient/deficient		Take a daily supplement containing 340 IU/day	



North of England
Commissioning Support Unit

There are currently two licensed preparations of vitamin D3 (colecalfiferol 20 micrograms, 800 IU) available :

- **Desunin®** (tablets) - an 800 units tablet also licensed for the prevention and treatment of vitamin D deficiency. It does not contain any gelatine, peanut oil or soybean oil. The tablets contain colecalfiferol that has been extracted from the wool of live, healthy sheep – this may be acceptable to vegetarians.
- **Fultium D3®** - is a product licensed for the prevention and treatment of vitamin D deficiency. It is available in 800 or 3200 or 20000 unit strength, and 2740 IU/ml oral drops). Excipients include gelatine, glycerol and previously contained arachis oil. The gelatine is halal and kosher compliant. (N.B. some of previous arachis oil containing preparation may still be in circulation).

As of May 2015 there are now 4 high strength colecalfiferol products which are licensed as medicines now available in the UK:

- Fultium D3® 20,000 IU capsules
- Aviticol® 20,000 IU capsules
- InVita D3® 25,000 unit/ml oral solution
- Plenachol® 20,000 IU capsules

There are also two unlicensed (both are made in the UK but classed as food supplements not medicinal products) 20,000unit products available on the formulary:

- **ProD3** products all contain colecalfiferol (Vitamin D3) which has been extracted from sheep's wool. The liquid is free of alcohol and polyethylene glycol. The capsules do not contain gelatine. The manufacturer states that the products are halal approved for Muslim patients, and are suitable for vegetarians. The ProD3 range can be ordered by pharmacies from the usual distributors (AAH, Phoenix,) or can be supplied directly to the pharmacy.
- **HuxD3** is a colecalfiferol product. The capsule shell is made of modified corn starch, glycerol (from a vegetarian source) and carrageen. The manufacturer states that the capsule contents are certified halal and kosher. The capsule can be squeezed open or chewed for those that cannot swallow. The product is formulated in sunflower oil. It is available from all mainline wholesalers.



North of England
Commissioning Support Unit

UK guidelines recommend a loading regime to provide a total of approximately 300,000 IU vitamin D given as a weekly or daily dose over 6 to 12 weeks in patients with vitamin D deficiency.

In view of the lack of evidence to classify monitoring requirements, clinicians should endeavour to:

1. Detect those who remain deficient after loading
2. Detect those who become deficient during maintenance
3. Detect those patients in whom vitamin D therapy uncovers sub-clinical primary hyperparathyroidism N.B. vitamin D treatment can unmask previously undiagnosed primary hyperparathyroidism, individuals thought to be at risk should be monitored by measurement of adjusted serum calcium levels.

Vitamin D toxicity

When the vitamin D dose is very high (usually as a result of inappropriate high-dose treatment or accidental overdosing) vitamin D toxicity may present as chronic hypocalcaemia. There is some evidence that vitamin D below 10,000IU/day is not usually associated with toxicity, but doses equal to or above 50,000 IU/day for several weeks or months are frequently associated with toxicity. The European Food Safety Authority has recently concluded that an upper limit of 4000IU (100µg) a day is safe for those over 11 years of age.

Specialist advice should be sought before vitamin D therapy is commenced in patients with tuberculosis and active sarcoidosis, and care should be taken in those with active nephrolithiasis.



Vitamin D deficiency / Insufficiency – Licensed Products							
Product	Dose		Cost per dose	Cost of 7 week treatment course of 40,000IU per week	Comments	Use in children	Use in Pregnancy/Breast-feeding
1st choice							
Fultium D3 [®] Capsules 20,000 IU	<p>Adult: Treatment of Deficiency - Two capsules weekly for 7 weeks (14 caps)</p> <p>Child 12-18yrs old: Treatment of Deficiency – One capsule every 2 weeks for 6 weeks (4 caps)</p>	£29 for 30 caps	97p	£13.58	<ul style="list-style-type: none"> • Licensed • Excipients include gelatine, and glycerol. The gelatine is halal and kosher compliant. • Not suitable for vegetarians or vegans. • Does not contain peanut oil or soya. 	Not recommended in children <12 years old	Not recommended
Fultium D3 [®] Capsules 3200 IU	<p>Adult & Elderly: One capsule daily for 12 weeks</p>	£13.32 for 30 caps	-	-	<ul style="list-style-type: none"> • Licensed • Excipients include gelatine, and glycerol. The gelatine is halal and kosher compliant. • Not suitable for vegetarians or vegans. • Does not contain peanut oil or soya as of Aug 2014. Previous batches prior to this did contain peanut oil and as such were contra-indicated in peanut oil or soya allergy. 	Not recommended in children <12 years old	Licensed during pregnancy and breast-feeding Treatment of vitamin D deficiency – 1 capsule (3,200 IU) daily
Fultium D3 [®] Capsules 800 IU	<p>Adult & Elderly: Treatment of deficiency - 1 – 5 capsules (800 – 4000 IU) daily. Long term maintenance therapy following treatment of deficiency 1 – 2 capsules (800 – 1600 IU) daily.</p>	£3.60 for 30 caps	-	-	<ul style="list-style-type: none"> • Licensed • Excipients include gelatine, and glycerol. The gelatine is halal and kosher compliant. • Not suitable for vegetarians or vegans. • Does not contain peanut oil or soya as of Aug 2014. Previous batches prior to this did contain peanut oil and as such were contra- 	Not recommended in children <12 years old	Licensed during pregnancy and breast-feeding Treatment of vitamin D deficiency =



North of England
Commissioning Support Unit

	<p>Child >12yrs old: Vitamin D deficiency or insufficiency in children over 12 years – 1 capsule daily depending on the severity of the disease and the patient's response to treatment.</p>				indicated in peanut oil or soya allergy.		<p>1 – 5 capsules (800 – 4000 IU) daily.</p> <p>Long term maintenance therapy following treatment of deficiency = 1 – 2 capsules (800 – 1600 IU) daily.</p>
<p>Fultium D3® Oral Drops 2740 IU/ml (3 drops = 200 IU)</p>	<p>Adult: Treatment of deficiency 12 – 60 drops (800 – 4,000 IU) daily.</p> <p>Child >0yrs old: see SPC</p>	£10.70 for 25ml	n/a	n/a	<ul style="list-style-type: none"> • Licensed • Does not contain peanut oil or soya. 	Licensed from 0 years old	<p>Licensed during pregnancy and breast-feeding</p> <p>Treatment of vitamin D deficiency = 6 – 60 drops (400 – 4,000 IU) daily.</p> <p>Long term maintenance therapy following treatment of deficiency AND Prevention of vitamin D deficiency = 6 – 30 drops (400 – 2,000 IU) daily.</p>



Alternatives							
Aviticol [®] Capsules 20,000 IU	<p>Adult: Treatment of Deficiency - Two capsules weekly for 7 weeks (14 caps)</p> <p>Child 12-18yrs old: Treatment of Deficiency – One capsule every 2 weeks for 6 weeks (4 caps)</p>	£29 for 30 caps	97p	£13.58	<ul style="list-style-type: none"> • Licensed • Not suitable for vegetarians or vegans. • Does not contain peanut oil or soya. 	Not recommended in children <12 years old	Not recommended
Desunin tablets 800 IU	<p>Adults & adolescents: Insufficiency - Recommended dose: One tablet per day.</p> <p>Higher dosed can be necessary to achieve desirable serum levels of 25-hydroxycoleciferol (25(OH)D).</p> <p>The daily dose should not exceed 5 tablets.</p>	£3.60 for 30 caps	-	-	<ul style="list-style-type: none"> • Licensed • May be suitable for vegetarians • Does not contain peanut oil or soya. 	Not recommended in children <12 years old	Desunin should be used during pregnancy, only in the case of a vitamin D deficiency... daily intake should not exceed 600 IU see SPC
Plenachol [®] 40,000 IU capsules	<p>Adult: Treatment of Deficiency - One capsule weekly for 7 weeks (7 caps)</p>	£15.00 for 10 caps	£1.50	£10.50	<ul style="list-style-type: none"> • Licensed • Free from gelatin, soya, gluten and peanut oil. Suitable for vegetarians, Halal and Kosher certified. • Does not contain peanut oil or soya. 	Use 20,000 unit strength	Not recommended
Plenachol [®] 20,000 IU capsules	<p>Adult: Treatment of Deficiency - Two capsules weekly for 7 weeks (14 caps)</p> <p>Child 12-18yrs old: Treatment of Deficiency – One</p>	£9 for 10 capsules	90p	£12.60	<ul style="list-style-type: none"> • Licensed • Free from gelatin, soya, gluten and peanut oil. Suitable for vegetarians, Halal and Kosher certified. • Does not contain peanut oil or soya. 	Not recommended in children <12 years old	Not recommended



	capsule every 2 weeks for 6 weeks (4 caps)						
Invita D3 [®] Oral solution 25,000 IU/ml	<p>Adult: Treatment of Deficiency – 25,000 IU (1ml) twice a week for 7 weeks</p> <p>Child 0-18yrs old: Prevention of deficiency 0-1 years 25000 IU (1 ampoule) every 8 weeks</p> <p>Prevention of deficiency 1-18 years 25000 IU (1 ampoule) every 6 weeks</p> <p>Treatment of deficiency 0-18 years 25000 IU (1 ampoule) once every 2 weeks for 6 weeks (followed by maintenance therapy of 400-1000 IU/day)</p>	£4.45 for 3 x 1ml amps	£1.48	£20.72	<ul style="list-style-type: none"> • Licensed • Colecalciferol is derived from live sheep's wool fat – the company has confirmed the product is suitable for vegetarians. • Does not contain peanut oil or soya. 	Licensed from 0 years old	Not recommended
Invita D3 [®] Oral solution 2400 IU/ml	<p>Paediatric posology: - prevention of deficiency 0-1 years 400 IU/day (6 drops) - prevention of deficiency 1-18 years 600 IU/day (9 drops)</p> <p>Pregnancy and breast-feeding posology: - prevention of deficiency 400 IU/day (6 drops)</p>	£3.60 for 10ml	n/a	n/a	<ul style="list-style-type: none"> • Licensed • Colecalciferol is derived from live sheep's wool fat – the company has confirmed the product is suitable for vegetarians. • Does not contain peanut oil or soya. 	Licensed from 0 years old	Licensed for use. Dose suggested for prevention of deficiency 400 IU/day (6 drops)



North of England
Commissioning Support Unit

Vitamin D deficiency / Insufficiency – Unlicensed Products							
Product	Dose		Cost per dose	Cost of 7 week treatment course of 40,000IU per week	Comments	Use in children	Use in Pregnancy/Breast-feeding
Pro D3 Capsules 20,000 IU	Adult: Deficiency - Two capsules weekly for 7 weeks (14 caps)	£23.99 for 30 caps	80p	£11.20	<ul style="list-style-type: none">• Unlicensed• Halal and suitable for vegetarians• Does not contain peanut oil or soya.		Not recommended
Hux D3 Capsules 20,000 IU	Adult: Deficiency - As above	£3.93 for 30 caps	13p	£1.82	<ul style="list-style-type: none">• Unlicensed• Halal and kosher, suitable for vegetarians• Does not contain peanut oil or soya.		Not recommended

All prices based on February 2015 DM+D prices except Plenachol® (prices from manufacturer)



North of England
Commissioning Support Unit

References

(Adapted from a piece of work originally completed by the RDTC)

1. Holick MF et al, *High prevalence of vitamin D inadequacy and implications for health*. Mayo Clin Proc, 2006. **81**: p. 353-73.
2. Ginde AA et al, *Prospective study of serum 25-hydroxyvitamin D-level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults*. J Am Geriatr Soc 2009. **57**: p. 1591-603.
3. Farrar, M.D., et al., *Efficacy of a dose range of simulated sunlight exposures in raising vitamin D status in South Asian adults: implications for targeted guidance on sun exposure*. Am J Clin Nutr. **97**(6): p. 1210-6.
4. Macdonald, H.M., et al., *Sunlight and dietary contributions to the seasonal vitamin D status of cohorts of healthy postmenopausal women living at northerly latitudes: a major cause for concern?* Osteoporos Int. **22**(9): p. 2461-72.
5. Sinha, A., T.D. Cheetham, and S.H. Pearce, *Prevention and treatment of vitamin D deficiency*. Calcif Tissue Int. **92**(2): p. 207-15.
6. Mavroeydi, A., et al., *Seasonal 25-hydroxyvitamin D changes in British postmenopausal women at 57 degrees N and 51 degrees N: a longitudinal study*. J Steroid Biochem Mol Biol. **121**(1-2): p. 459-61.
7. Ashwell, M., et al., *UK Food Standards Agency Workshop Report: an investigation of the relative contributions of diet and sunlight to vitamin D status*. Br J Nutr. **104**(4): p. 603-11.
8. *National Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. April 2013.*
9. *Fultium D3 SPC. Accessed via <https://www.medicines.org.uk/emc/medicine/25664/SPC/Fultium-D3+800IU+capsules/> on 07/03/14.*
10. *Desunin SPC. Accessed via <https://www.medicines.org.uk/emc/medicine/27007/SPC/Desunin+800+IU+Tablets/> on 07/03/14.*
11. *Pro D3 product information. Accessed via <http://www.prod3.co.uk/> on 07/03/14.*
12. *European Food Safety Authority: Upper Intake levels reviewed for vitamin D and calcium. 2012 Accessed via <http://www.efsa.europa.eu/en/press/news/120727a.htm> on 10/03/14.*
13. *UKMi Q&A 387.4 Which vitamin D preparations are suitable for a vegetarian or vegan diet? Date prepared: 18th February 2015 (partial update: 13th May 2015)*
14. *UKMi Q&A 82.3 What dose of vitamin D should be prescribed for the treatment of vitamin D deficiency? Date prepared: 7th April 2015*
15. *UKMi Q&A 384.3 Is there a suitable vitamin D product for a patient with a peanut or soya allergy? Date prepared: 2 May 2013*
16. *Fultium D3. Personal communication with Internis Pharmaceuticals Ltd on 15/07/14*
17. *Plenachol SPC. Accessed via <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1436500187460.pdf> on 15/07/15*



Suggested Doses of vitamin D for treatment of vitamin D deficiency in adults & children (Ref 14)

Dosing	Adult	Child
Treatment	<p><i>Treatment of vitamin D deficiency</i> Loading regimen up to a total of approximately 300,000 units given as weekly or daily split doses e.g.</p> <ul style="list-style-type: none"> • 50,000 unit capsules, one given weekly for 6 weeks • 20,000 unit capsules, two given weekly for 7 weeks • 800 unit capsules, five a day given for 10 weeks <p><i>Malabsorption states or liver disease</i> Often requires higher doses of up to 1mg (40,000 units) daily</p> <p><i>Treatment of hypocalcaemia due to hypoparathyroidism</i> Up to 5mg (200,000 units daily)</p>	<p><i>Treatment of vitamin D deficiency</i> 12-18 years: 20,000 units once every 2 weeks for 6 weeks</p> <p><i>Vitamin D deficiency in intestinal malabsorption or chronic liver disease</i> Orally or IM 1-12 years: 10,000-25,000 units/day 12-18 years: 10,000-40,000 units/day</p> <p><i>Oral treatment of rickets</i> 1-6 months: 3,000 units/day 6 months-12 years: 6,000 units/day 12-18 years: 10,000 units/day</p> <p><i>Treatment of vitamin D resistant rickets or hypoparathyroidism</i> Orally 20,000-100,000 units daily</p>
Maintenance	<p>Consider 1 month after loading with doses equivalent to 800 to 2,000units daily (occasionally up to 4,000units daily), given daily or intermittently at a higher equivalent dose</p>	<p><i>Oral prevention of rickets</i> Premature babies: 400 units once daily All other ages: 600 units once daily</p> <p><i>Prevention of vitamin D deficiency</i> 12-18 years: 20,000 units every 6 weeks</p>