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Search...



Anaemia - B12 and folate deficiency

Last revised in July 2015

Changes

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Last revised in July 2015

July 2015 — minor update. The section on prescribing issues has been amended to reflect the fact that cyanocobalamin tablets are no longer listed in Part XVIII B of the Drug Tariff, hence prescriptions no longer need to be endorsed with 'SLS' (Selected List Scheme).

November 2014 — minor update. Text about how and when to check for an underlying cause of vitamin B12 deficiency such as pernicious anaemia has been amended to be in line with the British Journal of Haematology *Guidelines for the diagnosis and treatment of cobalamin and folate disorders* [Devalia et al, 2014 (</anaemia-b12-and-folate-deficiency#!references/-314396>)].

February 2013 — reviewed. A literature search was conducted in January 2013 to identify evidence-based guidelines, UK policy, systematic reviews, and key RCTs published since the last revision of the topic. No major changes to clinical recommendations have been made.

[Previous changes](#)[Back to top](#)

January 2011 — topic structure revised to ensure consistency across CKS topics — no changes to clinical recommendations have been made.

January 2009 — minor update. Summary of Product Characteristics for Neo-cytamen® (hydroxocobalamin) updated to include information regarding monitoring platelets. Prescribing information has been updated. Issued in February 2009.

December 2007 to April 2008 — converted from CKS guidance to CKS topic structure. The evidence-base has been reviewed in detail, and recommendations are more clearly justified and transparently linked to the supporting evidence.

There are no major changes to the recommendations.

The topic has been retitled as it covers in detail the management of vitamin B₁₂ and folate deficiency anaemia, but not other causes of macrocytic anaemia. New sections have been included on how to investigate and when to refer a person with vitamin B₁₂ or folate deficiency anaemia.

October 2005 — minor technical update. Issued in November 2005.

July 2005 — updated to incorporate the *Referral guidelines for suspected cancer* published by the National Institute for Health and Clinical Excellence. Issued in July 2005.

August 2004 — reviewed. Validated in November 2004 and issued in February 2005.

July 2001 — reviewed. Validated in November 2001 and issued in April 2002.

October 2000 — updated to incorporate the Department of Health Referral Guideline for Suspected Upper Gastrointestinal Cancer.

January 1999 — written. Validated in March 1999 and issued in May 1999.

Update

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New evidence

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Evidence-based guidelines

No new evidence-based guidelines since 1 January 2013.

HTAs (Health Technology Assessments)

No new HTAs since 1 January 2013.

Economic appraisals

No new economic appraisals relevant to England since 1 January 2013.

Systematic reviews and meta-analyses

No new systematic reviews published since 1 January 2013.

Primary evidence

No new randomized controlled trials published in the major journals since 1 January 2013.

New policies

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No new national policies or guidelines since 1 January 2013.

New safety alerts

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No new safety alerts since 1 January 2013.

Changes in product availability

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No changes in product availability since 1 January 2013.

Goals

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- To establish the diagnosis of B12 and folate deficiency anaemia
- To treat B12 and folate deficiency anaemia effectively

Outcome measures

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- Normalized haemoglobin and blood picture

Definition

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What is it?

- The World Health Organization defines anaemia as [[WHO et al, 2001 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - In men over 15 years of age: haemoglobin (Hb) concentration less than 13 g/100 mL.
 - In non-pregnant women over 15 years of age: Hb concentration less than 12 g/100 mL.
 - In children 12–14 years of age: Hb concentration less than 12 g/100 mL.
 - In pregnant women: Hb concentration less than 11 g/dL.
 - A UK guideline on the management of iron deficiency in pregnancy states that an Hb level of 11 g/100 mL or more appears adequate in the first trimester, and a level of 10.5 g/100 mL appears adequate in the second and third trimesters [[Pavord et al, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

- However, there is variability between the criteria for iron deficiency anaemia between different studies and the normal range for Hb differs between different populations in the UK, so it seems reasonable to use the lower limit of the local laboratory normal range to define anaemia [[Goddard et al, 2011 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Deficiency of vitamin B12 or folate is the most frequent cause of megaloblastic anaemia [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
 - Megaloblastic anaemia is characterized by larger than normal developing red blood cells in the bone marrow (macrocytosis), with immature nuclei due to defective DNA (deoxyribonucleic acid) synthesis. Macrocytosis is an increase in the mean red cell volume to above the normal range (greater than 95 femtolitres).
 - For causes of non-megaloblastic macrocytic anaemia, see [Differential diagnosis \(/anaemia-b12-and-folate-deficiency#!diagnosissub:4\)](#).

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Causes

What causes it?

Vitamin B12 deficiency

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- Body stores of vitamin B12 are in the region of 2–3 mg. This is sufficient to last for 2–4 years [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Vitamin B12 combines with intrinsic factor (IF), which is produced by parietal cells in the stomach, to form an IF–B12 complex. The complex binds to surface receptors for IF in the distal ileum, which then allows absorption of vitamin B12 to take place [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- [Pernicious anaemia \(/anaemia-b12-and-folate-deficiency#!backgroundsub:3\)](#) (an autoimmune disorder which results in reduced production of IF) is the most common cause of vitamin B12 deficiency in the UK [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Other causes of vitamin B12 deficiency are rare, but include [[Hoffbrand, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - Gastric causes (for example gastrectomy, gastric resection, atrophic gastritis, *H.Pylori* infection, or congenital intrinsic factor deficiency or abnormality).
 - Inadequate dietary intake of vitamin B12 (for example vegan diet).
 - Intestinal causes (for example malabsorption, ileal resection, Crohn's disease affecting the ileum, chronic tropical sprue, HIV [due to abnormal small intestinal flora], or radiotherapy to the cervix [causing irradiation of the ileum]).
 - Drugs (for example colchicine, neomycin, metformin, or anticonvulsants).
 - Long-term use of drugs that affect gastric acid production (such as H₂-receptor antagonists and proton pump inhibitors) can worsen deficiency because gastric acid is needed to release vitamin B12 bound to proteins in food [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Pernicious anaemia

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- Pernicious anaemia is a autoimmune process that involves gastritis, atrophy of all layers of both the body and fundus of the stomach, and loss of normal gastric glands, mucosal architecture, and parietal and chief cells. These cause achlorhydria (absence of gastric hydrochloric acid) and lack of intrinsic factor.
 - Antibodies to intrinsic factor are very specific for pernicious anaemia, but are only present in around half of cases.
 - Anti-parietal cell antibodies are less specific; they occur in 85–90% of people with pernicious anaemia, but are also found in many people who do not have pernicious anaemia (for example people with atrophic gastritis and older people).
 - For more information on diagnosing pernicious anaemia, and testing for antibodies to intrinsic factor and parietal cells, see [Assessing B12 deficiency \(/anaemia-b12-and-folate-deficiency#!scenariorecommendation:1\)](#).
- The peak age of occurrence of pernicious anaemia is 60 years of age, and the female to male ratio is 1.6:1. Family history is positive in around 30% of cases.
- People with pernicious anaemia are at increased risk of developing gastric cancer, and there is an association with other autoimmune diseases (including primary myxoedema, thyrotoxicosis, Hashimoto's disease, Addison's disease, and vitiligo).

[[Hoffbrand et al, 2001 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Schick and Besa, 2011 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]

Folate deficiency

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- Folate is usually absorbed through the upper part of the small intestine and body stores are only sufficient for around 4 months [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Folate deficiency can occur for a number of reasons, including [[Hoffbrand, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [British Columbia Medical Association, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - **Dietary deficiency** (for example due to alcoholism or dietary fads).
 - **Malabsorption** (for example due to coeliac disease, tropical sprue, congenital specific malabsorption, jejunal resection, or inflammatory bowel disease).
 - **Excessive requirements**, for example due to:
 - Pregnancy.
 - Prematurity and infancy.
 - Malignancy (for example leukaemia, carcinoma, or lymphoma).
 - Blood disorders (for example haemolytic anaemias, sickle cell anaemia, thalassaemia major, or myelosclerosis).

- Inflammation (for example tuberculosis, Crohn's disease, or malaria).
- Metabolic disorders (for example homocystinuria).
- **Excessive urinary excretion** (for example due to congestive heart failure, acute liver damage, or chronic dialysis).
- **Drugs:**
 - With uncertain mechanism of action (for example anticonvulsants, and possibly alcohol and nitrofurantoin).
 - Causing malabsorption of folate (for example colestyramine, sulfasalazine, or methotrexate).
 - Trimethoprim may exacerbate pre-existing folate deficiency, but does not cause megaloblastic anaemia.

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Prevalence

How common is it?

- Pernicious anaemia accounts for 80% of cases of megaloblastic anaemia [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- A cross-sectional study of 3511 people, 65 years of age or older, investigated the prevalence of vitamin B12 and folate deficiency (with or without anaemia) [[Clarke et al, 2004 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - The prevalence of vitamin B12 deficiency was around 5% in people 65–74 years of age, and more than 10% in people 75 years of age or older.
 - The prevalence of folate deficiency was similar to that of vitamin B12 deficiency.
 - Of people with low vitamin B12 levels, only 10% had low folate levels.
- Dietary vitamin B12 deficiency is unusual in younger people, except those eating strict long-term vegan diets [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

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Complications

What are the complications?

- **Complications of anaemia:**
 - Adults with severe anaemia are at risk of cardiopulmonary complications [[AHRQ, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- **Complications of vitamin B12 deficiency:**
 - Neurological changes can occur, even when there are no changes in the blood count [[Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. These include paraesthesia, ataxia, peripheral neuropathy (the legs are usually affected more than the arms), visual disturbance, psychiatric abnormalities, and memory loss [[Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. [Subacute combined degeneration of the spinal cord \(/anaemia-b12-and-folate-deficiency#!diagnosissub:2/-314275\)](#) can cause a number of neurological signs.
 - Vitamin B12 deficiency predisposes to neural tube defects (such as spina bifida, anencephaly, and encephalocele) in the fetus. Incidence of neural tube defects increases with decreasing

serum vitamin B12 levels [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

- **Complications of folate deficiency:**

- Maternal folate deficiency in pregnancy is associated with neural tube defects and prematurity [[Hoffbrand, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. For more information on folic acid supplementation in pregnancy, see the CKS topic on [Pre-conception - advice and management \(/pre-conception-advice-and-management\)](#).
- Folate deficiency may be associated with cardiovascular disease and some cancers [[British Columbia Medical Association, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

- **Complications that can occur with either vitamin B12 or folate deficiency:**

- Nutritional deficiency of vitamin B12 or folate may cause ineffective production of any types of blood cells derived from bone marrow [[Sinning and Berliner, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Vitamin B12 or folate deficiency may cause sterility. This is reversible with appropriate vitamin supplementation [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Diagnosis

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How should I diagnose vitamin B12 or folate deficiency anaemia?

Diagnosis of anaemia caused by vitamin B12 or folate deficiency is made through [history \(/anaemia-b12-and-folate-deficiency#!diagnosissub:1\)](#), [examination \(/anaemia-b12-and-folate-deficiency#!diagnosissub:2\)](#), and [investigations \(/anaemia-b12-and-folate-deficiency#!diagnosissub:3\)](#), including taking a full blood count, blood film, and measuring serum concentrations of vitamin B12 and folate.

Symptoms

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What are the symptoms?

- **Symptoms of anaemia include:**

- Fatigue and lethargy.
 - Dyspnoea.
 - Faintness.
 - Palpitations.
 - Headache.
 - Tinnitus.
 - Anorexia.
 - Angina (if the person has pre-existing coronary artery disease).
- **Suspect vitamin B12 deficiency** if the person reports unexplained neurological symptoms (for example paraesthesia, numbness, cognitive changes, or visual disturbance).
 - **Suspect folate deficiency** if the person reports mild symptoms of peripheral neuropathy or psychiatric disturbance (for example depression).

Basis for recommendation

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Anaemia

- Information on the symptoms of anaemia are based on expert opinion in a textbook [[Longmore et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Vitamin B12 and folate deficiency

- Information on the specific symptoms of vitamin B12 deficiency and folate deficiency are based on expert opinion in a Canadian guideline [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a review article [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Signs

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What are the signs?

- **Signs of anaemia:**

- Pallor.
- If anaemia is severe (haemoglobin less than 8 g/100 mL), signs of a hyperdynamic circulation may be present (for example tachycardia or flow murmurs), sometimes progressing to heart failure.

- **Signs of vitamin B12 deficiency:**

- 'Lemon tinge' to skin (due to pallor and haemolysis-induced jaundice). This is usually of gradual onset.
- Glossitis (red, sore tongue).
- Oropharyngeal ulceration.
- Neuropsychiatric: irritability, depression, psychosis, and dementia.
- Neurological: impaired responses to vibration, touch, pain, and position; visual disturbance; and abnormal gait.
 - Subacute combined degeneration of the spinal cord has an insidious onset with peripheral neuropathy. Typically, joint position and vibration sense are first to be affected. Later, lower limb weakness and ataxia occur if the person is not treated.
 - The classic triad of signs associated with subacute combined degeneration of the spinal cord is extensor plantar reflexes, brisk knee jerks, and absent ankle jerks.

- **Signs of folate deficiency:**

- Mild peripheral neuropathy.
- Psychiatric changes (such as depression).

Basis for recommendation

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Anaemia

- Information on the typical signs associated with anaemia is based on expert opinion in a review article [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a medical textbook [[Longmore et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Vitamin B12 deficiency

- Information on the typical signs of vitamin B12 deficiency is based on expert opinion in review articles [[Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a medical textbook [[Longmore et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Folate deficiency

- Information on the typical signs of folate deficiency is based on expert opinion in review articles [[Hoffbrand, 2003 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Investigations

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What are the investigations?

- Check the [full blood count \(/anaemia-b12-and-folate-deficiency#!diagnosisadditional/-510900\)](#).
- **If the haemoglobin level is low and the mean cell volume (MCV) is high**, check serum vitamin B12 and serum folate concentrations. Red cell folate can also be used to screen for folate deficiency. See [Interpreting results of investigations \(/anaemia-b12-and-folate-deficiency#!diagnosisadditional\)](#).
- **If the haemoglobin level is low and the MCV is normal or low**, check ferritin, vitamin B12, and folate levels.
 - Conditions such as iron deficiency anaemia or thalassaemia trait can mask the development or presence of macrocytosis. For more information, see the CKS topic on [Anaemia - iron deficiency \(/anaemia-iron-deficiency\)](#).
- Generally, the diagnosis should rely on the clinical situation and the vitamin B12 and folate levels. A [blood film \(/anaemia-b12-and-folate-deficiency#!diagnosisadditional/-510900\)](#) may be useful in certain cases if there is diagnostic uncertainty. Discuss with a haematologist before requesting.
- Consider requesting liver function tests, gamma-glutamyl transpeptidase, and/or thyroid function tests if other causes of macrocytosis (for example excessive alcohol intake or hypothyroidism) are suspected.
- When interpreting results, use local laboratory reference ranges.

Interpreting results of investigations

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Full blood count

- As the mean cell volume (MCV) increases, the probability of vitamin B₁₂ and folate deficiency increases, especially if the MCV is 130 femtolitres or more (except if the person is taking hydroxycarbamide).
- If the MCV is 100–110 femtolitres, macrocytosis is more likely to be related to causes other than vitamin B12 deficiency (for example excessive alcohol intake, liver disease, anti-neoplastic drugs, HIV, and certain haematological conditions).

Blood film

- If the person has a vitamin B12 or folate deficiency anaemia (or megaloblastic anaemia of other cause):
 - The blood film will typically show oval macrocytes and hypersegmented nuclei in neutrophils (six or more lobes).
 - There may be a low reticulocyte count in relation to the degree of anaemia.
 - The white cell count and platelet count may be reduced if the anaemia is severe.

Vitamin B12

- Serum vitamin B12 levels are usually very low in megaloblastic anaemia or neuropathy due to vitamin B12 deficiency.
- However, incorrect interpretation of vitamin B12 levels can lead to the wrong diagnosis and inappropriate investigations or referral to hospital.
- Interpret the results of the serum vitamin B12 test taking into account clinical symptoms and the following limitations:
 - The test measures total, not metabolically active, vitamin B12.
 - The levels are not easily correlated with clinical symptoms, although people with vitamin B12 levels of less than 75 picomol/L (approximately 100 nanograms/L) usually have clinical or metabolic evidence of vitamin B12 deficiency. In most people with vitamin B12 deficiency, the serum vitamin B12 level is below 150 picomol/L (approximately 200 nanograms/L).
 - There is a large 'grey zone' between normal and abnormal levels and reference values (and units) may vary between laboratories.
 - Clinically significant vitamin B12 deficiency may be present even with vitamin B12 levels in the normal range, especially in elderly people.
 - Rare cases of false normal vitamin B12 results have been reported in the presence of high titres of anti-intrinsic factor antibody in people with megaloblastic anaemia or subacute combined degeneration of the cord. Therefore, the diagnosis of vitamin B12 deficiency should also include evaluation of the person's clinical state and other laboratory findings.
 - Testing for anti-intrinsic factor antibodies is therefore recommended in people with strong clinical features of B12 deficiency, such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal serum vitamin B12 level.
 - Women taking oral contraceptives may show decreased blood vitamin B12 levels because of a decrease in cobalamin carrier protein, rather than a deficiency state.
 - Vitamin B12 levels may be falsely low in pregnant women because of the increased plasma volume of pregnancy rather than actual deficiency of vitamin B12. This makes it practically very difficult to diagnose vitamin B12 deficiency in pregnancy.

Folate

- Serum and red cell folate levels are both low if the megaloblastic anaemia is due to folate deficiency. If there is no concurrent deficiency of vitamin B12, the red cell folate level may be helpful (the red cell folate concentration can also be low in vitamin B12 deficiency, so it is more difficult to interpret the significance of a low red cell count than serum folate concentration).
- False results of red cell folate levels can also occur if the person has had a recent blood transfusion. This is because the red cell folate concentration will reflect the concentration in the transfused cells.
- Haemolysis during venesection releases folate from red cells and invalidates the serum folate assay (for example leading to spuriously normal results in deficient patients).

Basis for recommendation

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Recommendations for investigating macrocytic anaemia and interpreting the results are based on expert opinion in the British Journal of Haematology *Guidelines for the diagnosis and treatment of cobalamin and folate disorders* [Devalia et al, 2014 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], a Best Practice review [Smellie et al, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], an article on the pitfalls of testing for macrocytosis [Galloway and Hamilton, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], an article on macrocytic anaemias in the ABC of Clinical Haematology [Hoffbrand and Provan, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], a guidebook (*Nutritional Anaemia*) [Badham et al, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], a textbook chapter on macrocytic and megaloblastic anaemias [Hoffbrand et al, 2001 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], as well as expert opinion from reviewers of this CKS topic.

- People who have a macrocytic anaemia should have their vitamin B12 and folate levels checked [Smellie et al, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].
- Serum vitamin B12 and folate assays are the most widely-used screening tests for these deficiencies. If serum concentration is low, this implies deficiency, but it is possible to have a low serum concentration in the absence of pronounced physiological deficiency (for example vitamin B₁₂ levels are reduced by pregnancy, and by recent poor dietary intake of folate) [Hoffbrand and Provan, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].

Reference ranges

- CKS has not included reference ranges as the normal range for haemoglobin differs between different populations in the UK, and normal values for vitamin B12 and folate tests may differ slightly with different commercial kits [Hoffbrand et al, 2006 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))]. In view of this, it seems reasonable to use local laboratory reference ranges.

Full blood count and blood film

- The recommendation to perform a full blood count and blood film is based on expert opinion in national guidelines [[Goddard et al, 2011 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], review articles [[Hoffbrand et al, 2001 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a textbook [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Vitamin B12 serum concentration

- The recommendation for the interpretation of vitamin B12 serum concentrations is based on expert opinion in the British Journal of Haematology guidelines [[Devalia et al, 2014 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], review articles [[Hoffbrand et al, 2001 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a Canadian guideline [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Folate serum concentration

- The recommendation for the interpretation of folate concentrations is based on expert opinion from a review article and a textbook [[Hoffbrand et al, 2001 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

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Differential diagnosis

What else might it be?

- Vitamin B12 and folate deficiencies are not the only causes of macrocytosis.
- Other (non-megaloblastic) causes of macrocytosis include:
 - Alcohol — may cause macrocytosis with neither anaemia nor a change in liver function.
 - Drugs (such as hydroxycarbamide and azathioprine).
 - Severe thyroid deficiency — a modest increase in mean cell volume may be seen.
 - Pregnancy and the neonatal period.
 - Haematological abnormalities such as:
 - Myelodysplasia — progressive bone marrow failure, with variable changes seen in the quantity and quality of red blood cells, white blood cells, and platelets.
 - Aplastic anaemia — pancytopenia is noted (reduction in the numbers of circulating red blood cells, white blood cells, and platelets).
 - Pure red cell aplasia.
 - Plasma protein changes (for example myeloma).
- If the cause of the macrocytic anaemia is uncertain, blood film analysis may help (for example a uniform macrocytosis is often found with alcohol excess, target cells with liver disease, and polychromasia with haemolysis).

Information on the differential diagnosis of macrocytosis is based on expert opinion from review articles [[Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and a text book [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Scenario: Management

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Scenario: Management of anaemia - vitamin B12 and folate deficiency

Age from 16 years onwards

Assessment

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How should I assess a person with vitamin B12 or folate deficiency anaemia?

Assessment should include determining the underlying cause of [vitamin B12 \(/anaemia-b12-and-folate-deficiency#!scenariorecommendation:1\)](#) or [folate \(/anaemia-b12-and-folate-deficiency#!scenariorecommendation:2\)](#) deficiency.

Assessing B12 deficiency

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How should I investigate a person with vitamin B12 deficiency anaemia in primary care?

- Determine whether there is an underlying [cause \(/anaemia-b12-and-folate-deficiency#!backgroundsub:2\)](#) for the serum vitamin B12 deficiency (for example pernicious anaemia), by checking for serum anti-intrinsic factor antibodies.
 - Note that testing for anti-intrinsic factor antibodies is recommended in people with strong clinical features of B12 deficiency, such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal vitamin B12 level. For more information, see the section on [Interpreting results of investigations \(/anaemia-b12-and-folate-deficiency#!diagnosisadditional\)](#).
 - Checking for gastric anti-parietal cell antibodies is no longer recommended to diagnose pernicious anaemia.
- Determine whether the person has experienced [complications \(/anaemia-b12-and-folate-deficiency#!backgroundsub:6\)](#) of anaemia, or of vitamin B12 deficiency.

Basis for recommendation

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The recommendations about checking for an underlying cause for B12 deficiency are based on expert opinion in the British Journal of Haematology *Guidelines for the diagnosis and treatment of cobalamin and folate disorders* [[Devalia et al, 2014 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and an article on macrocytic anaemias in the ABC of Clinical Haematology [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Checking for anti-intrinsic factor antibodies

- Anti-intrinsic factor antibody is extremely specific for pernicious anaemia, with a high positive predictive value of 95%, but a low sensitivity of 40–60%. This means that about half of people with pernicious anaemia will have anti-intrinsic factor antibody [[Andres et al, 2004 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Longmore et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. If anti-intrinsic factor antibody is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia [[Devalia et al, 2014 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- The recommendation about checking for anti-intrinsic factor antibodies in people with a normal serum B12 level if there are strong clinical features of B12 deficiency to check for pernicious anaemia is based on expert opinion in *Guidelines for the diagnosis and treatment of cobalamin and folate disorders* published by the British Journal of Haematology [[Devalia et al, 2014 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Not checking for gastric anti-parietal cell antibodies

- Anti-parietal cell antibody is found in 80% of people with pernicious anaemia, but also in 10% of people without it. However, it has a low specificity of about 50%, which is much lower than that of anti-intrinsic factor antibody [[Andres et al, 2004 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. If anti-parietal cell antibody is not present it is unlikely that the person has pernicious anaemia, but its presence is not diagnostic as it can occur in other conditions (for example atrophic gastritis) and older people (16% of normal women over 60 years of age) [[Carmel, 1992 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. As a result, it is no longer recommended as a diagnostic test for pernicious anaemia [[Devalia et al, 2014 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Assessing for folate deficiency

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How should I investigate a person with folate deficiency anaemia in primary care?

- Determine whether there is an underlying [cause \(/anaemia-b12-and-folate-deficiency#!backgroundsub:4\)](#) for the folate deficiency.
 - If folate levels are low, and the history suggests malabsorption, check for coeliac disease with anti-endomysial or anti-transglutaminase antibodies (depending on the local laboratory).
- Determine whether the person has experienced [complications \(/anaemia-b12-and-folate-deficiency#!backgroundsub:6\)](#) of anaemia or folate deficiency.

Basis for recommendation

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This recommendation is based on an article on macrocytic anaemias in the ABC of Clinical Haematology [[Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], a textbook chapter on megaloblastic and other macrocytic anaemias [[Hoffbrand et al,](#)

[2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and a patient pathway on anaemia [NHS Scotland, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].

Referral

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When should I refer a person with vitamin B12 or folate deficiency anaemia?

- Seek urgent advice from a haematologist if the person has neurological symptoms, or is pregnant.
 - Refer to a haematologist if the cause of vitamin B12 or folate deficiency is uncertain following investigations, or the suspected cause is haematological malignancy (urgently refer) or other blood disorder.
 - Refer to a gastroenterologist if:
 - Malabsorption of vitamin B12 (other than due to pernicious anaemia) or folate is suspected.
 - The person has pernicious anaemia and gastrointestinal symptoms, especially if there is a suspicion of gastric cancer (for example co-existing iron deficiency). The urgency of referral will depend on the nature of the symptoms.
 - The person is folate deficient, and antibody testing suggests coeliac disease (positive for anti-endomysial or anti-transglutaminase antibodies).
 - Consider referral to a dietician if vitamin B12 or folate deficiency is thought to be due to a poor diet.
-

Basis for recommendation

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These recommendations are pragmatic advice based on an anaemia patient pathway [NHS Scotland, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], a chapter from the ABC of clinical haematology on macrocytic anaemias [Hoffbrand and Provan, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))], and guidelines from the National Institute for Health and Clinical Excellence on referral for suspected cancer [NICE, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].

- People with pernicious anaemia have an increased risk of gastric carcinoma or gastric polyps (2–3 times more common than in age- and sex-matched controls) [Hoffbrand and Provan, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))]. CKS considered this information and expert opinion from reviewers of this CKS topic when making the recommendation about when to refer to a gastroenterologist.
- Further tests which may be considered by specialists if the cause of vitamin B12 deficiency is uncertain include [Hoffbrand and Provan, 2007 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))]:
 - Radioactive vitamin B12 absorption studies.
 - Bone marrow examination (to exclude myelodysplasia, aplastic anaemia, myeloma, or other marrow disorders associated with macrocytosis).
 - Endoscopy and gastric biopsy (vitamin B12 deficiency) or duodenal biopsy (folate deficiency).

Treatment for B12 deficiency

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How should I treat a person with vitamin B12 deficiency anaemia?

- **For people with neurological involvement:**

- Seek urgent specialist advice from a haematologist.
- Ideally, management should be guided by a specialist, but if specialist advice is not immediately available, consider the following:
 - Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, then administer hydroxocobalamin 1 mg intramuscularly every 2 months.

- **For people with no neurological involvement:**

- Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days for 2 weeks.
- Maintenance dose (where the vitamin B12 deficiency is not thought to be diet related): administer hydroxocobalamin 1 mg intramuscularly every 3 months for life (standard dose). Note that the manufacturers' licence is for every 2–3 months.
- Maintenance dose (where vitamin B12 deficiency is thought to be diet related): advise people either to take oral cyanocobalamin tablets 50–150 micrograms daily between meals, or have a twice-yearly hydroxocobalamin 1 mg injection. The injection regimen may be preferred in the elderly (who are more likely to have malabsorption), and vegans (as currently available brands of oral cyanocobalamin may not be suitable for vegans).
 - In vegans, this treatment may need to be life-long, whereas in other people with dietary deficiency replacement treatment can be stopped once the vitamin B12 levels have been corrected and the diet has improved.
 - Advise people to eat foods rich in vitamin B12. Foods which have been fortified with vitamin B12 (for example some soy products, and some breakfast cereals and breads) are good alternative sources to meat, eggs, and dairy products.
 - For more information about using vitamin B12 products, see [Prescribing information \(/anaemia-b12-and-folate-deficiency#!prescribinginfo\)](#).

Basis for recommendation

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- **Vitamin B12 replacement treatment**

- Vitamin B12 replacement therapy is a well established standard treatment and this recommendation is supported by the British National Formulary [[BNF 64, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], Summaries of Product Characteristics (SPCs) [[ABPI Medicines Compendium, 2002 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [ABPI Medicines Compendium, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], a Canadian guideline [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and expert opinion in medical textbooks [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Hydroxocobalamin is preferred to cyanocobalamin in the UK. This is because hydroxocobalamin can be given at maintenance dose intervals of up to 3 months, as it is

retained in the body for longer [[BNF 64, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

• Dietary advice

- The recommendation on vitamin B12 fortified foods is based on information from the national Expert Group on Minerals and Vitamins [[Expert Group of Vitamins and Minerals Secretariat, 2002 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], a guidebook (*Nutritional Anaemia*) [[Badham et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and on expert opinion from medical textbooks [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Expert feedback suggests that dietary changes are unlikely to have an effect in the majority of people with pernicious anaemia.

Symptoms persist despite maintenance vitamin B12 treatment

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What if a person is still symptomatic despite maintenance vitamin B12 treatment?

- If a person's symptoms recur before the next injection is due, seek specialist advice from a haematologist.

Basis for recommendation

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- Some experts acknowledge that there is a small group of patients who report a recurrence of their symptoms earlier than 3 monthly.
 - CKS could find no guidelines or evidence on the management of this group.
 - Feedback from expert reviewers differs with regard to whether or not more frequent intramuscular injections of hydroxocobalamin 1 mg are required, and if they are, what regimen to suggest.
 - In the absence of evidence and expert consensus, CKS suggest seeking specialist advice in this situation.

Treatment for folate deficiency

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How should I treat a person with folate deficiency anaemia?

- Give dietary advice: good sources of folate are broccoli, Brussels sprouts, asparagus, peas, chickpeas, and brown rice.
- Prescribe oral folic acid 5 mg daily.
- Check vitamin B12 levels in all people before starting folic acid, as treatment can improve well-being such that it can mask underlying B12 deficiency and allow neurological disease to develop.
- In most people, treatment will be required for 4 months. However, folic acid may need to be taken

for longer (sometimes for life) if the underlying cause of deficiency is persistent.

- For information on folic acid supplementation in pregnancy, see the CKS topic on [Pre-conception - advice and management \(/pre-conception-advice-and-management\)](#).

Basis for recommendation

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- The examples of good dietary sources of folate are from the Food Standards Agency [[Food Standards Agency, 2008 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Folic acid supplementation is a well-established, standard treatment for folate deficiency, and this recommendation is supported by the British National Formulary [[BNF 64, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], a Canadian guideline [[British Columbia Medical Association, 2013 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and expert opinion in medical textbooks [[Hoffbrand et al, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [Hoffbrand and Provan, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Treatment with folic acid usually results in a rapid improvement in symptoms. In most people, treatment will be needed for only 4 months, as poor diet is the most common cause [[BNF 64, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. Folic acid supplementation for 4 months brings about haematological remission and replenishes body stores.
- Vitamin B12 deficiency should be excluded before presuming that a macrocytic anaemia is due to a folate deficiency. If the underlying cause is actually vitamin B12 deficiency but treatment with more than 1 mg folic acid a day is given, this can give the impression that the anaemia has been successfully treated, but vitamin B12 neuropathy will progress and may become irreversible [[Badham et al, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].
- Concerns have been expressed in recent literature about the potential for harms with long-term supplementation with high folic acid doses [[Powers, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - A possible link has been found with folic acid and an increase in the progression rate of pre-cancerous lesions to cancer (particularly colorectal cancer). However, there is inadequate evidence from human trials to confirm this.

Monitoring

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What monitoring of vitamin B12 or folate deficiency treatment is recommended?

- A full blood count and reticulocyte count should be performed:
 - After approximately 10 days of treatment, to document the response.
 - A rise in the haemoglobin level, and an increase in the reticulocyte count to above the normal range, would be expected as a sign of a positive treatment effect.
 - If the person has vitamin B12 deficiency anaemia and there is no improvement with therapy, check serum folate level (if this has not already been done).
 - After 8 weeks, to confirm a normal blood count.
 - On completion of folic acid treatment, to confirm a response.

- Ongoing monitoring of people being treated with vitamin B12 or folic acid is generally considered unnecessary (unless a lack of compliance with folate treatment is suspected, or anaemia recurs).

Basis for recommendation

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These monitoring recommendations are based on available guidelines [[Hutchinson, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], a Best Practice Review [[Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], an article on the pitfalls of testing for macrocytosis [[Galloway and Hamilton, 2007 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], the British National Formulary [[BNF 64, 2012 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)], and pharmaceutical manufacturers advice [[ABPI Medicines Compendium, 2012a \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. Feedback from expert reviewers was also taken into account.

- The manufacturer states that regular monitoring of the blood is advisable, as hydroxocobalamin should not be given before a megaloblastic marrow has been demonstrated [[ABPI Medicines Compendium, 2012a \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. However, expert opinion in a Best Practice review is that people with pernicious anaemia who receive vitamin B12 replacement should not become vitamin B12 deficient, therefore in most cases further monitoring would seem unnecessary, although practices vary and some haematologists would recommend annual full blood counts [[Smellie et al, 2005 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

Prescribing issues

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What issues should I consider before prescribing vitamin B12?

- Intramuscular hydroxocobalamin injection is the treatment of choice for vitamin B12 deficiency in the UK.
 - Cyanocobalamin 50 microgram tablets can be prescribed in certain circumstances for people with vitamin B12 deficiency of dietary origin. Be aware that:
 - Only non-proprietary cyanocobalamin tablets can be prescribed on the NHS; Cytacon[®] tablets (branded cyanocobalamin tablets) are blacklisted and hence cannot be prescribed on the NHS.
 - Currently available brands of cyanocobalamin tablets may not be suitable for vegans.
- Vitamin B12 preparations should not be used to treat megaloblastic anaemia of pregnancy.

Adverse effects

- Adverse effects of vitamin B12 include nausea, headache, dizziness, fever, hot flushes, itching, and injection-site reactions.
- Cardiac arrhythmias secondary to hypokalaemia has been reported during the first few weeks of treatment. The manufacturers advise that plasma potassium levels should be monitored for the

first few weeks of use.

- Rarely, acneiform and bulbous eruptions have been reported.
- Very rarely, anaphylaxis has been reported. Regardless of whether the injection is administered at the surgery or at home, it is good practice to monitor the person for a few minutes afterwards in case of anaphylactic reaction.

Drug interactions

- Serum concentration of hydroxocobalamin may be reduced by concurrent administration of oral contraceptives. However, this interaction is unlikely to have clinical significance.
- Absorption of oral vitamin B12 may be reduced by 4-aminosalicylic acid, colchicine, biguanides, neomycin, colestyramine, potassium chloride, methyldopa, and cimetidine.

Basis for recommendation

These recommendations are based on the the British National Formulary (BNF) [[BNF 69, 2015 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)] and the manufacturers' Summaries of Product Characteristics [[ABPI Medicines Compendium, 2012a \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [ABPI Medicines Compendium, 2012b \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]. The recommendation to monitor the person for a few minutes for anaphylactic reaction is based on a clinical guideline on the administration of vitamin B12 [[Hutchinson, 2006 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

- According to the BNF [[BNF 69, 2015 \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)]:
 - 'Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B12 of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months'.
 - Non-proprietary cyanocobalamin tablets are considered by the Joint Formulary Committee to be less suitable for prescribing as a first-line treatment; however, its use may be justifiable in certain circumstances.
- The manufacturers advice that hydroxocobalamin and cyanocobalamin should not be used to treat megaloblastic anaemia of pregnancy, as megaloblastic anaemia in pregnancy is due to folate deficiency [[ABPI Medicines Compendium, 2012a \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#); [ABPI Medicines Compendium, 2012b \(/anaemia-b12-and-folate-deficiency#!references/-314396\)](#)].

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Advice about vitamin B12

What advice should I give to people about vitamin B12?

- The dosage depends on the specific illness and how much the condition improves once treatment has started. When the condition has improved sufficiently, the dose will be reduced, although some people will require regular injections for the rest of their lives.
- Advise the person that:
 - They will need to return to their health care professional for the intramuscular injections. The frequency of this will depend on the prescribed dose.
 - If they have cardiovascular disease, their blood potassium levels in particular will need to be

monitored at the start of treatment.

- They may need regular blood monitoring. The frequency of this will depend on their compliance with treatment, response to treatment, and the advice of their haematologist.

Basis for recommendation

These recommendations are based on the the British National Formulary [BNF 64, 2012 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))] and the manufacturers' Summaries of Product Characteristics [ABPI Medicines Compendium, 2012a ([/anaemia-b12-and-folate-deficiency#!references/-314396](#)); ABPI Medicines Compendium, 2012b ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].

- Cardiac arrhythmias secondary to hypokalaemia have been reported during initial therapy and plasma potassium should, therefore, be monitored during this period [ABPI Medicines Compendium, 2012a ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].
- The manufacturer states that regular monitoring of the blood is advisable, as hydroxocobalamin should not be given before a megaloblastic marrow has been demonstrated [ABPI Medicines Compendium, 2012a ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))]. However, expert opinion in a Best Practice review is that people with pernicious anaemia who receive vitamin B12 replacement should not become vitamin B12 deficient, therefore in most cases further monitoring would seem unnecessary, although practices vary and some haematologists would recommend annual full blood counts [Smellie et al, 2005 ([/anaemia-b12-and-folate-deficiency#!references/-314396](#))].

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Search strategy

Scope of search

A literature search was conducted for guidelines, systematic reviews and randomized controlled trials on primary care management of Anaemia - B12 and folate deficiency

Search dates

April 2008 – January 2013

Key search terms

Various combinations of searches were carried out. The terms listed below are the core search terms that were used for Medline.

- exp Anemia/, anemia.tw., anaemia.tw., AND exp Vitamin B12 Deficiency or exp Vitamin B12/, deficien\$.tw., folate.tw., exp Folic Acid/

Table 1 . Key to search terms.

Search commands	Explanation
/	indicates a MeSh subject heading with all subheadings selected

.tw	indicates a search for a term in the title or abstract
exp	indicates that the MeSH subject heading was exploded to include the narrower, more specific terms beneath it in the MeSH tree
\$	indicates that the search term was truncated (e.g. wart\$ searches for wart and warts)

Sources of guidelines

- [National Institute for Health and Care Excellence \(NICE\) \(http://www.nice.org.uk\)](http://www.nice.org.uk)
- [Scottish Intercollegiate Guidelines Network \(SIGN\) \(http://www.sign.ac.uk\)](http://www.sign.ac.uk)
- [Royal College of Physicians \(http://www.rcplondon.ac.uk/\)](http://www.rcplondon.ac.uk/)
- [Royal College of General Practitioners \(http://www.rcgp.org.uk/\)](http://www.rcgp.org.uk/)
- [Royal College of Nursing \(http://www.rcn.org.uk/development/practice/clinicalguidelines\)](http://www.rcn.org.uk/development/practice/clinicalguidelines)
- [NICE Evidence \(https://www.evidence.nhs.uk/topics/\)](https://www.evidence.nhs.uk/topics/)
- [Health Protection Agency \(http://www.hpa.org.uk\)](http://www.hpa.org.uk)
- [World Health Organization \(http://www.who.int\)](http://www.who.int)
- [National Guidelines Clearinghouse \(http://www.guideline.gov\)](http://www.guideline.gov)
- [Guidelines International Network \(http://www.g-i-n.net\)](http://www.g-i-n.net)
- [TRIP database \(http://www.tripdatabase.com\)](http://www.tripdatabase.com)
- [GAIN \(http://www.gain-ni.org/index.php/audits/guidelines\)](http://www.gain-ni.org/index.php/audits/guidelines)
- [NHS Scotland National Patient Pathways \(http://www.pathways.scot.nhs.uk/\)](http://www.pathways.scot.nhs.uk/)
- [New Zealand Guidelines Group \(http://www.nzgg.org.nz\)](http://www.nzgg.org.nz)
- [Agency for Healthcare Research and Quality \(http://www.ahrq.gov/\)](http://www.ahrq.gov/)
- [Institute for Clinical Systems Improvement \(http://www.icsi.org\)](http://www.icsi.org)
- [National Health and Medical Research Council \(Australia\) \(http://www.nhmrc.gov.au/publications/index.htm\)](http://www.nhmrc.gov.au/publications/index.htm)
- [Royal Australian College of General Practitioners \(http://www.racgp.org.au/your-practice/guidelines/\)](http://www.racgp.org.au/your-practice/guidelines/)
- [British Columbia Medical Association \(http://www.health.gov.bc.ca/gpac/index.html\)](http://www.health.gov.bc.ca/gpac/index.html)
- [Canadian Medical Association \(http://www.cma.ca/index.php/ci_id/54316/la_id/1.htm\)](http://www.cma.ca/index.php/ci_id/54316/la_id/1.htm)
- [Alberta Medical Association \(http://www.topalbertadoctors.org/cpgs.php\)](http://www.topalbertadoctors.org/cpgs.php)
- [University of Michigan Medical School \(http://ocpd.med.umich.edu/cme/self-study/\)](http://ocpd.med.umich.edu/cme/self-study/)
- [Michigan Quality Improvement Consortium \(http://mqic.org/guidelines.htm\)](http://mqic.org/guidelines.htm)
- [Singapore Ministry of Health \(http://www.moh.gov.sg/content/moh_web/home/Publications/guidelines/cpg.html\)](http://www.moh.gov.sg/content/moh_web/home/Publications/guidelines/cpg.html)
- [National Resource for Infection Control \(http://www.nric.org.uk\)](http://www.nric.org.uk)
- [Patient UK Guideline links \(http://www.patient.co.uk/guidelines.asp\)](http://www.patient.co.uk/guidelines.asp)
- [UK Ambulance Service Clinical Practice Guidelines \(http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/jrcalc_2006/guidelines/\)](http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/jrcalc_2006/guidelines/)
- [RefHELP NHS Lothian Referral Guidelines \(http://www.refhelp.scot.nhs.uk/index.php?option=com_content&task=view&id=490&Itemid=104\)](http://www.refhelp.scot.nhs.uk/index.php?option=com_content&task=view&id=490&Itemid=104)
- Medline (with guideline filter)
- [Driver and Vehicle Licensing Agency \(http://www.dft.gov.uk/dvla/medical/atag glance.aspx\)](http://www.dft.gov.uk/dvla/medical/atag glance.aspx)
- [NHS Health at Work \(http://www.nhshealthatwork.co.uk/oh-guidelines.asp\)](http://www.nhshealthatwork.co.uk/oh-guidelines.asp) (occupational health

practice)

Sources of systematic reviews and meta-analyses

- [The Cochrane Library \(http://www.thecochranelibrary.com\)](http://www.thecochranelibrary.com) :
 - Systematic reviews
 - Protocols
 - Database of Abstracts of Reviews of Effects
- Medline (with systematic review filter)
- EMBASE (with systematic review filter)

Sources of health technology assessments and economic appraisals

- [NIHR Health Technology Assessment programme \(http://www.hta.ac.uk/\)](http://www.hta.ac.uk/)
- [The Cochrane Library \(http://www.thecochranelibrary.com\)](http://www.thecochranelibrary.com) :
 - NHS Economic Evaluations
 - Health Technology Assessments
- [Canadian Agency for Drugs and Technologies in Health \(http://www.cadth.ca\)](http://www.cadth.ca)
- [International Network of Agencies for Health Technology Assessment \(http://www.inahta.org\)](http://www.inahta.org)

Sources of randomized controlled trials

- [The Cochrane Library \(http://www.thecochranelibrary.com\)](http://www.thecochranelibrary.com) :
 - Central Register of Controlled Trials
- Medline (with randomized controlled trial filter)
- EMBASE (with randomized controlled trial filter)

Sources of evidence based reviews and evidence summaries

- [Bandolier \(http://www.medicine.ox.ac.uk/bandolier/\)](http://www.medicine.ox.ac.uk/bandolier/)
- [Drug & Therapeutics Bulletin \(http://dtb.bmj.com/\)](http://dtb.bmj.com/)
- [TRIP database \(http://www.tripdatabase.com\)](http://www.tripdatabase.com)
- [Central Services Agency COMPASS Therapeutic Notes \(http://www.medicinesni.com/courses/type.asp?ID=CN\)](http://www.medicinesni.com/courses/type.asp?ID=CN)

Sources of national policy

- [Department of Health \(http://www.dh.gov.uk\)](http://www.dh.gov.uk)
- Health Management Information Consortium (HMIC)

Patient experiences

- [Healthtalkonline \(http://www.healthtalkonline.org/\)](http://www.healthtalkonline.org/)
- [BMJ - Patient Journeys \(http://www.bmj.com/bmj-series/patient-journeys\)](http://www.bmj.com/bmj-series/patient-journeys)
- [Patient.co.uk - Patient Support Groups \(http://www.patient.co.uk/selfhelp.asp\)](http://www.patient.co.uk/selfhelp.asp)

Sources of medicines information

The following sources are used by CKS pharmacists and are not necessarily searched by CKS information specialists for all topics. Some of these resources are not freely available and require subscriptions to access content.

- [British National Formulary \(http://www.evidence.nhs.uk/formulary/bnf/current\)](http://www.evidence.nhs.uk/formulary/bnf/current) (BNF)
- [electronic Medicines Compendium \(http://www.medicines.org.uk\)](http://www.medicines.org.uk) (eMC)
- [European Medicines Agency \(http://www.ema.europa.eu/ema/\)](http://www.ema.europa.eu/ema/) (EMA)

- [LactMed \(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT\)](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT)
- [Medicines and Healthcare products Regulatory Agency \(http://www.mhra.gov.uk/index.htm\)](http://www.mhra.gov.uk/index.htm) (MHRA)
- [REPROTOX \(http://www.reprotox.org/Default.aspx\)](http://www.reprotox.org/Default.aspx)
- [Scottish Medicines Consortium \(http://www.scottishmedicines.org.uk/Home\)](http://www.scottishmedicines.org.uk/Home)
- [Stockley's Drug Interactions \(https://www.medicinescomplete.com/mc/stockley/current/login.htm?uri=http%3A%2F%2Fwww.medicinescomplete.com%2Fmc%2Fstockley%2Fcurrent%2F\)](https://www.medicinescomplete.com/mc/stockley/current/login.htm?uri=http%3A%2F%2Fwww.medicinescomplete.com%2Fmc%2Fstockley%2Fcurrent%2F)
- [TERIS \(http://depts.washington.edu/terisweb/teris/\)](http://depts.washington.edu/terisweb/teris/)
- [TOXBASE \(http://www.toxbase.org/\)](http://www.toxbase.org/)
- [Micromedex \(http://www.micromedex.com/products/hcs/\)](http://www.micromedex.com/products/hcs/)
- [UK Medicines Information \(http://www.ukmi.nhs.uk/\)](http://www.ukmi.nhs.uk/)

Anaemia - B12 and folate deficiency - Summary [Back to top](#)

- Deficiency of vitamin B12 or folate is the most common cause of megaloblastic anaemia.
- Megaloblastic anaemia is characterized by larger than normal developing red blood cells in the bone marrow, with immature nuclei due to defective DNA synthesis. This results in larger than normal red blood cells (macrocytosis).
- Pernicious anaemia (an autoimmune disorder which results in reduced production of intrinsic factor) is the most common cause of vitamin B12 deficiency in the UK. Other causes of vitamin B12 deficiency are rare, but include:
 - Gastric causes (e.g. gastrectomy, gastric resection).
 - Inadequate dietary intake of vitamin B12 (e.g. vegan diet).
 - Intestinal causes (e.g. malabsorption, ileal resection, Crohn's disease).
 - Drugs (e.g. colchicine, neomycin, metformin, anticonvulsants).
- Folate deficiency can occur for a number of reasons, including:
 - Dietary deficiency.
 - Malabsorption.
 - Excessive requirements:
 - Pregnancy, prematurity, and infancy.
 - Malignancy (e.g. leukaemia, carcinoma, lymphoma).
 - Blood disorders (e.g. haemolytic anaemias).
 - Inflammation (e.g. tuberculosis, Crohn's disease).
 - Metabolic causes (e.g. homocystinuria).
 - Excessive urinary excretion (e.g. chronic dialysis).
 - Drugs (e.g. anticonvulsants, colestyramine, sulfasalazine, methotrexate).
- Diagnosis of anaemia caused by vitamin B12 or folate deficiency is made through history, examination, and investigations, including taking a full blood count, blood film, and measuring serum concentrations of vitamin B12 and folate.
 - If vitamin B12 deficiency is found, serum anti-intrinsic factor antibodies should be checked.
 - If there are strong clinical features of B12 deficiency such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal serum vitamin B12 level, serum anti-intrinsic factor antibodies should also be checked.

- If folate levels are low, and the history suggests malabsorption, tests for anti-endomysial or anti-transglutaminase antibodies should be done (depending on the local laboratory) to check for coeliac disease.
- Treatment of B12 deficiency in people with neurologic involvement includes:
 - Seeking urgent specialist advice from a haematologist.
 - Management should ideally be guided by a specialist, but if specialist advice is not immediately available, initially treatment with hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, then hydroxocobalamin 1 mg intramuscularly every 2 months should be considered — where B12 deficiency is *not* thought to be diet related.
- Treatment of B12 deficiency in people with no neurologic involvement includes:
 - Initial treatment with hydroxocobalamin 1 mg intramuscularly on alternate days for 2 weeks.
 - Maintenance treatment with hydroxocobalamin 1 mg intramuscularly every 3 months for life — where B12 deficiency is *not* thought to be diet related, or
 - Maintenance treatment with oral cyanocobalamin tablets or a twice-yearly hydroxocobalamin 1 mg injection — where vitamin B12 deficiency is thought to be diet related.
- Treatment of folate deficiency includes:
 - Oral folic acid 5 mg daily. In most people, treatment will be required for 4 months. Folic acid may need to be taken longer term (sometimes for life) if the underlying cause of deficiency is persistent.
 - Dietary advice. Good sources of folate are broccoli, brussels sprouts, asparagus, peas, chickpeas, and brown rice.

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Have I got the right topic?

Age from 16 years onwards

This CKS topic covers the management of the most common macrocytic anaemias: vitamin B₁₂ deficiency anaemia (including pernicious anaemia) and folate deficiency anaemia.

This CKS topic does not cover the management of other causes of macrocytic anaemia, other types of anaemia, macrocytosis in the absence of anaemia, or vitamin B₁₂ deficiency or folate deficiency without anaemia.

There is a separate CKS topic on [Anaemia - iron deficiency \(/anaemia-iron-deficiency\)](#).

The target audience for this CKS topic is healthcare professionals working within the NHS in the UK, and providing first contact or primary health care.

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Diagnosis

Diagnosis of anaemia - B12 and folate deficiency

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Management

- **[Scenario: Management \(/anaemia-b12-and-folate-deficiency#!scenario\)](#)** : covers the management of anaemia caused by vitamin B12 or folate deficiency.

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Prescribing information

Important aspects of prescribing information relevant to primary healthcare are covered in this section specifically for the drugs recommended in this CKS topic. For further information on contraindications, cautions, drug interactions, and adverse effects, see the [electronic Medicines Compendium \(http://www.medicines.org.uk/emc\)](#) (eMC) (<http://medicines.org.uk/emc>), or the [British National Formulary \(http://www.evidence.nhs.uk/formulary/bnf/current\)](#) (BNF) .

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Evidence

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