## Cyanocobalamin Decision Document

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cyanocobalamin (Vitamin B12)</th>
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</thead>
<tbody>
<tr>
<td>Brands</td>
<td>Cyanocobalamin (all preparations including Cytacon tablets, Cytamen Injection)</td>
</tr>
<tr>
<td>Decision</td>
<td>West Essex CCG <strong>does not</strong> commission cyanocobalamin.</td>
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<tr>
<td>Date</td>
<td>29th August 2019</td>
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<tr>
<td>Evidence</td>
<td>Vitamins were included in the <strong>NHS England - Conditions for which over the counter items should not routinely be prescribed in primary care: Guidance for CCGs</strong> (29 March 2018)</td>
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</tbody>
</table>

Vitamins and minerals should not be routinely prescribed in primary care due to limited evidence of clinical effectiveness.

Exceptions:
- Medically diagnosed deficiency, including for those patients who may have a lifelong or chronic condition or have undergone surgery that results in malabsorption. Continuing need should however be reviewed on a regular basis. NB maintenance or preventative treatment is not an exception.
- Calcium and vitamin D for osteoporosis.
- Malnutrition including alcoholism (see **NICE guidance**)
- Patients suitable to receive Healthy start vitamins for pregnancy or children between the ages 6 months to their fourth birthday. (NB this is not on prescription but commissioned separately)

**British National Formulary**

### Anaemia, megaloblastic – overview

Most megaloblastic anaemias result from a lack of either vitamin B12 or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should not be instituted until the results of tests are available.

One cause of megaloblastic anaemia in the UK is pernicious anaemia in which lack of gastric intrinsic factor resulting from an autoimmune gastritis causes malabsorption of vitamin B12.

Vitamin B12 is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare syndrome of congenital transcobalamin II deficiency.

Vitamin B12 should be given prophylactically after total gastrectomy or total ileal resection (or after partial gastrectomy if a vitamin B12 absorption test shows vitamin B12 malabsorption).

Apart from dietary deficiency, all other causes of vitamin B12 deficiency are attributable to malabsorption.
There is little place for the use of low-dose vitamin B12 orally and none for vitamin B12 intrinsic factor complexes given by mouth. Vitamin B12 in larger oral doses [unlicensed] may be effective.

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. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B12 neuropathy.

**Guidelines for the diagnosis and treatment of cobalamin and folate disorders**

Devalia V, Hamilton MS, Molloy AM on behalf of the British Committee for Standards in Haematology (2014)

**Treatment of cobalamin deficiency**

**Recommendations**

1. Treatment of established cobalamin deficiency should follow the schedules in the BNF (Grade 1A).
2. Initial treatment with oral cobalamin may not be appropriate in pernicious anaemia, but may be considered in maintenance or correction of suboptimal levels in asymptomatic patients (Grade 2C)

Low dose oral cyanocobalamin (BNF, 50mcg) is licenced within the UK and may improve serum cobalamin and bio-chemical markers in borderline cases. Their role in the treatment of subclinical deficiency is under active research. Care must be taken if low dose supplements are prescribed; as such an approach risks the suboptimal treatment of latent and emerging pernicious anaemia with possible inadequate treatment of neurological features.

**Low serum cobalamin without anaemia or other significant objective parameters (low cobalamin of uncertain significance)**

**Recommendation**

1. In patients with serum cobalamin levels of ‘subclinical deficiency’ on two occasions, an empirical trial of treatment with oral cyanocobalamin (50mcg daily for 4 weeks) should be given. Strict instructions should be given to patients to seek immediate medical attention if symptoms of neuropathy develop. The cobalamin level should be rechecked after 3 months, and second-line tests considered if there is no improvement (Grade 2c).

**Oral vitamin B12 compared with intramuscular vitamin B12 for vitamin B12 deficiency**

Wang H, Li L, Qin L, Song Y, Vidal-Alaball J, Liu T. Cochrane Review CD004655 (Published 15 March 2018)

Two studies used 1000 μg/day oral vitamin B₁₂ and showed no relevant difference to intramuscularly applied vitamin B₁₂ with regard to vitamin B₁₂ blood levels. One trial used 2000 μg/day vitamin B₁₂ and showed higher vitamin B₁₂ blood levels in favour of oral vitamin B₁₂. Two studies reported side effects. One study stated that no treatment-related side effects were seen in both
the oral and intramuscular vitamin B\textsubscript{12} groups. One study reported that 2 of 30 participants in the oral vitamin B\textsubscript{12} group left the trial early due to side effects. Orally taken vitamin B\textsubscript{12} showed lower treatment-associated costs than intramuscular vitamin B\textsubscript{12} in one trial. No study reported on clinical signs and symptoms of vitamin B\textsubscript{12} deficiency (e.g. fatigue, depression, neurological complications), health-related quality of life, or acceptability of the treatment scheme.

Note: The above doses are NOT licenced in the UK.

**NICE CKS Anaemia – B\textsubscript{12} and folate deficiency** recommends oral cyanocobalamin tablets 50–150 micrograms daily between meals as **maintenance** for people where deficiency is thought to be diet related (in addition to dietary advice).

- **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 three times a week for 2 weeks.
  - The **maintenance** dose depends on whether the deficiency is diet related or not. For people with B\textsubscript{12} deficiency that is:
    - Not thought to be diet related
      - administer hydroxocobalamin 1 mg intramuscularly every 2–3 months for life.
    - 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.
      - In vegans, treatment may need to be life-long, whereas in other people with dietary deficiency replacement treatment can be stopped once the vitamin B\textsubscript{12} levels have been corrected and the diet has improved.

**Hunt et al. Vitamin B\textsubscript{12} deficiency BMJ 2014;349 4\textsuperscript{th} September 2014**

Mild deficiency manifests as fatigue and anaemia, with indices suggesting B\textsubscript{12} deficiency but an absence of neurological features. Moderate deficiency may include an obvious macrocytic anaemia with, for example, glossitis and some mild or subtle neurological features, such as distal sensory impairment. Severe deficiency shows evidence of bone marrow suppression, clear evidence of neurological features, and risk of cardiomyopathy. However, it is important to recognise that clinical features of deficiency can manifest without anaemia and also without low serum vitamin B\textsubscript{12} levels. In these cases treatment should still be given without delay.
Position Statement:

NHS West Essex Clinical Commissioning Group does not commission Cyanocobalamin.

Where Vitamin B12 is indicated, NHS West Essex commissions Hydroxocobalamin.

Recommendations:

- Treatment of Vitamin B12 deficiency (including functional deficiency) should follow the schedules in the BNF.\textsuperscript{3,4}

- Review all existing patients prescribed cyanocobalamin tablets. Where treatment is for prevention/maintenance, advise the patient that Vitamin B12 (oral) should be purchased.

- Identify all patients prescribed Cyanocobalamin Injection and advise either:
  - Hydroxocobalamin IM for treatment of deficiency (including functional deficiency) in line with \textit{BNF/NICE CKS} and maintenance patients where deficiency is not diet related
  - Oral Cyanocobalamin for prevention/maintenance (where deficiency is diet related) which can be purchased

- Note: if a prescriber has particular concerns that a patient might not be able to, or is unwilling to self-care and treatment with a medication is required, then a prescription (FP10) should be considered.

Rationale for recommendation

Effectiveness

Cyanocobalamin is listed as “Less suitable for prescribing” in the \textit{BNF}, which applies to preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing.

National funding/access decision\textsuperscript{2}

\textbf{NHS restrictions}

Cyanocobalamin solution and Cytamen\textsuperscript{®} injection are not prescribable in NHS primary care.

Scotland: drugs, medicines and other substances not to be ordered by contractors in the Provision of primary medical services under a general medical services contract

https://www.sehd.scot.nhs.uk/pca/PCA2010(M)22.pdf

Safety

Adverse effects\textsuperscript{1}

Adverse effects of cyanocobalamin include:

- Sensitisation (rarely) — itching exanthema, or exceptionally as anaphylactic shock.
- Acneform and bullous eruptions.

Pregnancy — cyanocobalamin should not be used to treat megaloblastic anaemia in pregnancy, as this is caused by folic acid deficiency.

Patient factors
Vitamin B12 deficiency is a common but serious condition
Clinical presentation may not be obvious thus leading to complex issues around diagnosis and treatment
There is no ideal test to define deficiency and therefore the clinical condition of patients is of the utmost importance
If the clinical features suggest deficiency then it is important to treat patients to avoid neurological impairment even if there may be discordance between the results and clinical features

References:
1. NICE CKS Anaemia - B12 and folate deficiency (Last Revised February 2019)
3. BNF [Accessed 17.7.19]

Acknowledgements:
Mid Essex CCG Policy Statement: Prescribing of Cyanocobalamin tablets is not supported (September 2018)