

PRESCRIBING INFORMATION

**CYANOCOBALAMIN INJECTION, USP
(Vitamin B12)**

1000 mcg/mL Sterile

Mylan Pharmaceuticals ULC
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**CYANOCOBALAMIN INJECTION, USP
(Vitamin B₁₂)**

**1000 mcg/mL Sterile
FOR INTRAMUSCULAR OR
DEEP SUBCUTANEOUS USE**

Hematopoietic

Pharmacology

Vitamin B₁₂ is a group of cobalt-containing B complex vitamins, also known as cobalamins, synthesized by microorganisms. Cyanocobalamin and hydroxocobalamin are the principle forms of vitamin B₁₂ in clinical use. They have equivalent vitamin B₁₂ activity.

In humans; exogenous source of vitamin B₁₂ is required for nucleoprotein and myelin synthesis, cell production, normal growth, and for the maintenance of normal erythropoiesis.

Pharmacokinetics

Absorption: Vitamins B₁₂ is irregularly absorbed from the distal small intestine following oral administration. Vitamin B₁₂ absorption is an active process that requires gastric intrinsic factor. Intrinsic factor is a glycoprotein secreted by the gastric mucosa. Passive diffusion through the intestinal wall can occur but large amounts of B₁₂ are required (i.e. >1 mg). Following oral doses less than 3 mcg, peak plasma concentrations are not reached for 8 to 12 hours because the vitamin is transiently retained in the wall of the lower ileum.

Vitamin B₁₂ is rapidly absorbed from intramuscular (IM) and subcutaneous (SC) sites of injection; peak plasma concentrations are reached within 1 hour after IM injection.

Distribution: Vitamin B₁₂ is distributed into the liver, bone marrow, and other tissues, including the placenta. At birth, the blood concentration of vitamin B₁₂ in neonates is 3 to 5 times that of the mother.

Total body stores of vitamin B₁₂ in healthy individuals are estimated to range from 1 to 11 mg, with an average of 5 mg; 50 to 90% is stored in the liver. Vitamin B₁₂ is believed to be converted to coenzyme form in the liver and is probably stored in tissues in this form.

Elimination: Following IM administration of 0.1 to 1 mg of cyanocobalamin, 50 to 90% of the dose may be excreted in urine by glomerular filtration within 48 hours, with the major portion being excreted in the first 8 hours. Hydroxocobalamin is more highly protein bound and is retained in the body longer than cyanocobalamin; however, it is not more effective in normalizing the hematocrit.

Because hydroxocobalamin may cause formation of antibodies to hydroxocobalamin transcobalamin II complex, cyanocobalamin is usually the preferred form of vitamin B₁₂.

Indications

Vitamin B₁₂ Deficiency: For Vitamin B₁₂ deficiency occurring in pernicious anemia with or without neurological complications. Other macrocytic, megaloblastic anemias where etiology

suggests malabsorption of vitamin B₁₂ such as; following gastrectomy, gastric carcinoma, megaloblastic anemia associated with such gastrointestinal disorders as sprue syndrome, blind loops and anastomoses and fish tapeworm.

Note: In macrocytic megaloblastic anemia of pregnancy and sprue syndromes, cyanocobalamin may fail to produce satisfactory response, folic acid being indicated alone or in combination with cyanocobalamin.

The injection is also suitable for use as the flushing dose in the Schilling (vitamin B₁₂ absorption) test for pernicious anemia.

Contraindications

Vitamin B₁₂ is contraindicated in patients who have experienced hypersensitivity reactions to the vitamin or to cobalt.

Warnings

Patients who have early Leber's disease (hereditary optic nerve atrophy) have been found to suffer severe and swift optic atrophy when treated with vitamin B₁₂.

Hypokalemia and sudden death may occur when severe megaloblastic anemia is treated intensively. Lack of therapeutic response may be due to infection, uremia, concomitant treatment with chloramphenicol or misdiagnosis.

Precautions

A sensitivity history should be obtained from the patient prior to administration of vitamin B₁₂; and intradermal test dose is recommended before vitamin B₁₂ is administered to patients known to be sensitive to cobalamins.

Parenteral administration of cyanocobalamin is the required treatment for originally diagnosed and relapsed pernicious anemia with severe neurologic manifestations. Also in treatment of megaloblastic anemia associated with sprue, supplementation with folic acid is usually necessary and parenteral vitamin B₁₂ may be required.

If a vitamin B₁₂ deficiency is allowed to progress more than 3 months, permanent degenerative spinal cord lesions may occur; such lesions have been observed when folic acid is used as the sole hematopoietic agent.

Patients who have early Leber's disease (hereditary optic nerve atrophy) have been found to suffer severe and swift optic nerve atrophy when treated with vitamin B₁₂.

Serum potassium concentrations should be monitored during early vitamin B₁₂ therapy and potassium administered if necessary, since fatal hypokalemia could occur upon conversion of megaloblastic anemia to normal erythropoiesis with vitamin B₁₂ as a result of increased erythrocyte potassium requirements. Therapeutic response to vitamin B₁₂ may be impaired by concurrent injection, uremia, concomitant treatment with chloramphenicol or misdiagnosis.

Cyanocobalamin or hydroxocobalamin should not be administered i.v.

Indiscriminate administration of vitamin B₁₂ may mask the true diagnosis of pernicious anemia. A dietary deficiency of only vitamin B₁₂ is rare. Multiple vitamin deficiency is expected in any dietary deficiency.

Children: Benzyl alcohol contained in some products has been associated with toxicity in newborns. Toxicity appears to have resulted from administration of large amounts of benzyl alcohol (100 to 400 mg/kg daily). Products containing benzyl alcohol should be used cautiously in neonates, especially those who are receiving other benzyl alcohol containing medications.

Drug Interactions: Most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B₁₂ diagnostic microbiological blood assays. Chloramphenicol may antagonize the hematopoietic response to vitamin B₁₂. Hematopoietic response in such patients should be monitored.

Colchicine, aminoglycosides, certain anticonvulsants (e.g., phenytoin, Phenobarbital, primidone), para-aminosalicylic acid or excessive alcohol intake for longer than 2 weeks may impair the absorption of vitamin B₁₂. Vitamin C may destroy vitamin B₁₂. Patients should avoid ingesting large amounts of vitamin C within 1 hour of oral vitamin B₁₂ administration.

Histamine₂-Receptor Antagonists (cimetidine, ranitidine, nizatidine, famotidine): May potentially cause vitamin B₁₂ deficiency by decreasing gastric acid cleavage of vitamin B₁₂ from food sources. This may be important in patients with low stores of vitamin B₁₂ or in patients taking H₂-antagonists for extended periods of time (>2 years).

Pregnancy: No adverse effects have been reported with ingestion of normal daily requirements during pregnancy.

Lactation: Vitamin B₁₂ is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B₁₂ concentration. No adverse effects have been reported with intake of normal daily requirements during lactation.

Adverse Effects

Vitamin B₁₂ is usually non toxic even in large doses. However, mild, transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, feeling of swelling of entire body, pulmonary edema and congestive heart failure early in treatment, anaphylactic shock and death have been reported following vitamin B₁₂ administration.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Dosage and Administrations

Administration:

Cyanocobalamin is usually administered by IM or deep subcutaneous injection. If the drug is administered subcutaneously, care should be taken to avoid injection into the dermis or upper subcutaneous tissue. *Because the drug is excreted more rapidly after IV injection, the IV route should be avoided.*

Dosage:

In patients with Addisonian (pernicious) anemia, parenteral therapy with cyanocobalamin is the recommended method of treatment and will be required for the remainder of the patient's life. Oral therapy is not dependable. Serum potassium must be watched closely the first 48 hours; and potassium should be replaced if necessary. Reticulocyte plasma count, vitamin B₁₂ and folic acid levels must be obtained prior to treatment and between the fifth and seventh day of therapy.

In patients with other types of vitamin B₁₂ deficiency due to malabsorption, the malabsorption should be corrected. In all patients a well balanced dietary intake should be prescribed and poor dietary habits should be corrected.

Vitamin B₁₂ Deficiency: For the treatment of vitamin B₁₂ deficiency in adults, the usual IM or subcutaneous dosage of cyanocobalamin is 30 to 100 mcg daily for 5-10 days. Once clinical symptoms have subsided and the blood components have returned to normal, monthly IM maintenance doses of 100 to 200 mcg appear to be sufficient to maintain a normoblastic bone marrow. Dosage should be adjusted as necessary to maintain normal hematologic morphology and an erythrocyte count greater than 4.5 million/nm³.

In the Schilling test, the flushing dose is 1000 mcg.

Supplied: Each ml contains: Cyanocobalamin 1,000 mcg, Sodium Acetate 0.5 mg, Glacial Acetic Acid 0.1 mg, Sodium Chloride 9.0 mg with Benzyl Alcohol 1.5 % as preservative in Water for Injection q.s.

Sodium Hydroxide and/or Hydrochloric Acid may have been used to adjust pH . Multiple dose vials of 10 ml and 30mL.

Store at room temperature 15°-30°C.PROTECT FROM LIGHT. Any unused portion should be used within 30 days of opening.

For therapeutic use only.

REFERENCES:

1. Prescribing Information: Vitamin B₁₂ Cyanocobalamin Injection USP 1000 mcg/mL Hematopoietic. Bioniche Pharma (Canada) Ltd. January 2002.

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