PRESCRIBING INFORMATION

CYANOCOBALAMIN INJECTION USP

(Vitamin B_{12})

Solution for Injection

1 000 mcg / mL

Hematopoietic

Hikma Canada Limited
5995 Avebury Road, Suite 804
Mississauga, Ontario
L5R 3P9

Date of Preparation:
April 20, 2022

Control Number: 262700

CYANOCOBALAMIN INJECTION USP

Solution for Injection, 1 000 mcg / mL

ACTION AND CLINICAL PHARMACOLOGY

Vitamin B_{12} is a group of cobalt-containing B complex vitamins, also known as cobalamins, synthesized by microorganisms. Cyanocobalamin and hydroxocobalamin are the principal forms of vitamin B_{12} in clinical use. They have equivalent vitamin B_{12} activity.

In humans; exogenous source of vitamin B_{12} is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and for the maintenance of normal erythropoiesis.

Pharmacokinetics

Absorption: Vitamin B_{12} is irregularly absorbed from the distal small intestine following oral administration. Vitamin B_{12} 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 B_{12} 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 B_{12} 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 B_{12} is distributed into the liver, bone marrow, and other tissues, including the placenta. At birth, the blood concentration of vitamin B_{12} in neonates is 3 to 5 times that of the mother.

Total body stores of vitamin B_{12} 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 B_{12} 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 B_{12}.

INDICATIONS AND CLINICAL USE

Vitamin B_{12} Deficiency: For vitamin B_{12} deficiency occurring in pernicious anemia with or without neurological complications. Other macrocytic, megaloblastic anemias where etiology suggests malabsorption of vitamin B_{12} 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 B_{12} absorption) test for pernicious anemia.

CONTRAINDICATIONS

Vitamin B_{12} 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 nerve atrophy when treated with vitamin B_{12}.

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 B_{12}; an intradermal test dose is recommended before vitamin B_{12} 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 B_{12} may be required.

If a vitamin B_{12} 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 B_{12}.

Serum potassium concentrations should be monitored during early vitamin B_{12} therapy and potassium administered if necessary, since fatal hypokalemia could occur upon conversion of megaloblastic anemia to normal erythropoiesis with vitamin B_{12} as a result of increased erythrocyte potassium requirements. Therapeutic response to vitamin B_{12} may be impaired by concurrent infection, uremia, concomitant treatment with chloramphenicol, or misdiagnosis.

Cyanocobalamin or hydroxocobalamin should not be administered intravenously (IV).

Indiscriminated administration of vitamin B_{12} may mask the true diagnosis of pernicious anemia. A dietary deficiency of only vitamin B_{12} is rare. Multiple vitamin deficiency is expected in any dietary deficiency.

Histamine$_2$-Receptor Antagonists (cimetidine, ranitidine, nizatidine, famotidine): May potentially cause vitamin B_{12} deficiency by decreasing gastric acid cleavage of vitamin B_{12} from food sources. This may be important in patients with low stores of vitamin B_{12} or in patients taking H_2-antagonists for extended periods of time (>2 years).

Special Populations

Pediatrics: 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.

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

Nursing Women: Vitamin B_{12} is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B_{12} concentration. No adverse effects have been reported with intake of normal daily requirements during lactation.

ADVERSE REACTIONS

Vitamin B_{12} is usually nontoxic even in large doses, however, mild transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, feeling of swelling of the entire body, pulmonary edema and congestive heart failure early in treatment, anaphylactic shock and death have been reported following vitamin B_{12} administration.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

DRUG INTERACTIONS

Most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic microbiological blood assays. Chloramphenicol may antagonize the hematopoietic response to vitamin B_{12}. 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 B_{12}. Vitamin C may destroy vitamin B_{12}. Patients should avoid ingesting large amounts of vitamin C within 1 hour of oral vitamin B_{12} administration.

DOSAGE AND AMINISTRATION

Administration

Cyanocobalamin is usually administered by intramuscular 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 intravenous injection, the IV route should be avoided.**

Dosage

In patients with Addisonian (pernicious) anemia, parenteral therapy with vitamin B_{12} 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 B_{12} 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 B_{12} deficiency due to malabsorption, the malabsorption should be corrected. In all patients a well-balanced dietary intake should be prescribed and prior dietary habits should be corrected.

Vitamin B_{12} Deficiency: For the treatment of vitamin B_{12} 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/nm^3.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of the 1 mL ampoule contains cyanocobalamin 1000 mcg, sodium chloride for isotonicity, sodium acetate as a buffer, acetic acid to adjust pH and water for injection.

Each mL of the 10 mL vial contains cyanocobalamin 1000 mcg, benzyl alcohol 1.5% as a preservative, sodium chloride, sodium acetate and acetic acid as buffers, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Cyanocobalamin Injection USP is available in amber glass single use ampoules of 1 mL, boxes of 10, and amber glass multidose vials of 10 mL, boxes of 1.

LATEX-FREE STOPPER: Vial stopper contains no dry natural rubber.

STORAGE AND STABILITY

Store between 15 and 30ºC. Protect from light.

Use vial within 28 days of first puncture when stored between 15 and 30ºC.

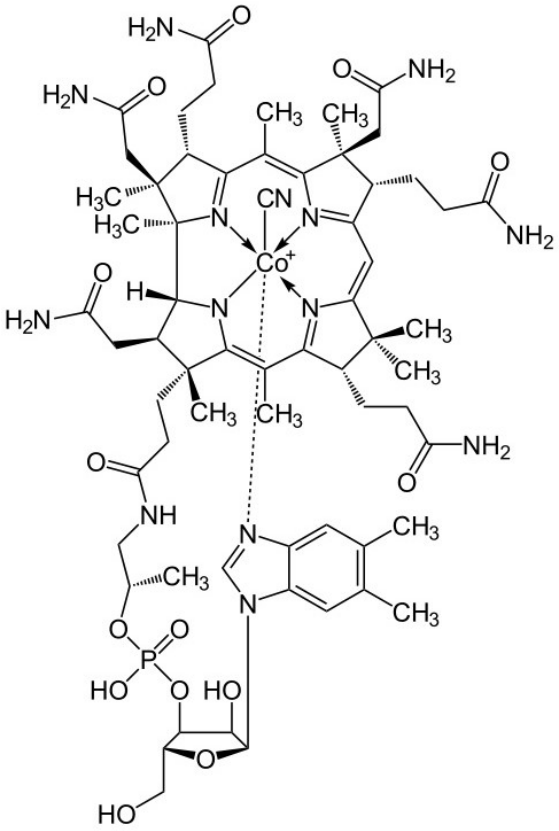
PHARMACEUTICAL INFORMATION

Proper name: Cyanocobalamin; Vitamin B_{12}

Chemical name: 5,6-dimethyl-benzimidazolyl cyanocobamide

Molecular formula and molecular weight: $C_{63}H_{88}CoN_{14}O_{14}P$; 1355.4 g/mol

Structural formula:



Physicochemical properties: Cyanocobalamin is a dark red, practically odourless, hygroscopic crystalline powder. It is sparingly soluble in water, soluble in alcohol, and insoluble in acetone, chloroform and ether. Aqueous solutions of cyanocobalamin are neutral.

REFERENCES

1. Sandoz Canada Inc., Prescribing Information, VITAMIN B_{12} (Cyanocobalamin Injection USP), 100 mcg/mL and 1000 mcg/mL, Control No. 099873, December 14, 2011.