VITAMIN B 12 (Systemic)

Introduction

This monograph includes information on the following:1) Cyanocobalamin; 2) Hydroxocobalamin b.

VA CLASSIFICATION (Primary/Secondary)¾VT110/DX900
Commonly used brand name(s):Alphamin2; Anacobin1; Bedoz1; Cobex1; Cobolin-M1; Crystamine1; Crysti-121; Cyanoject1; Cyomin1; Hydro-Cobex2; Hydro-Crysti-122; Hydrobexan2; Hydroxy-Cobal2; LA-122; NascobalÒ1; Neuroforte-R1; Primabalt1; Rubramin PC1; Shovite1; Vibal1; Vibal LA2; Vitabee 121.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

b Not commercially available in Canada.

Category

Nutritional supplement (vitamin); antianemic; diagnostic aid (vitamin B 12 deficiency).

Note: Vitamin B 12 (also known as the cobalamins) is a water-soluble vitamin.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Note: Indications for cyanocobalamin and hydroxocobalamin are the same, although hydroxocobalamin may be preferred for treatment of vitamin B 12 deficiency since optic neuropathies may degenerate with administration of cyanocobalamin. 1 However, some patients develop antibodies to the hydroxocobalamin-transcobalamin II complex. 6

Accepted

Anemia, pernicious (treatment)¾Vitamin B 12 is indicated for treatment of pernicious anemia (due to lack of or inhibition of intrinsic factor). 4

Vitamin B 12 deficiency (prophylaxis and treatment)¾Vitamin B 12 is indicated for prevention and treatment of vitamin B 12 deficiency.
Deficiency of vitamin B 12 may lead to macrocytic, megaloblastic anemia and possible irreversible neurologic damage. 2

Vitamin B 12 deficiency may occur as a result of inadequate nutrition or intestinal malabsorption but does not occur in healthy individuals receiving an adequate balanced diet. However, simple vitamin B 12 deficiency may occur in strict vegetarians (vegan-vegetarians) and their breast-fed infants 8 since vitamin B 12 1 is found in animal protein and not in vegetables. For prophylaxis of vitamin B 12

deficiency, dietary improvement, rather than supplementation, is advisable. For treatment of vitamin B 12 deficiency, supplementation is preferred. 19

Recommended intakes may be increased and/or supplementation may be necessary in the following conditions (based on documented vitamin B 12 deficiency):
Alcoholism 1, 28

Anemia, hemolytic 1

Fever, chronic
Fish tapeworm infestation 1

Gastrectomy
Gastritis, atropic with achlorhydria 29

Genetic disorders¾homocystinuria and/or methylmalonic aciduria 15, 16, 17, 18

Hepatic-biliary tract disease 1 ¾hepatic function impairment, alcoholism with cirrhosis
Hyperthyroidism 1

Intestinal diseases¾celiac, tropical sprue, regional enteritis, bacterial overgrowth of small intestine, persistent diarrhea, ileal resection 1, 7

Infection, prolonged
Malabsorption syndromes associated with pancreatic insufficiency 3

Malignancy of pancreas or bowel 1

Renal disease 1

Stress, prolonged

Some unusual diets (e.g., vegan-vegetarian, 1 macrobiotic, 21, 22 or reducing diets that drastically restrict food selection) may not supply minimum daily requirements of vitamin B 12.
Supplementation is necessary in patients receiving total parenteral nutrition (TPN) or undergoing rapid weight loss or in those with malnutrition, because of inadequate dietary intake.
Recommended intakes for all vitamins and most minerals are increased during pregnancy. Many physicians recommend that pregnant women receive multivitamin and mineral supplements, especially those pregnant women who do not consume an adequate diet and those in high-risk categories (i.e., women carrying more than one fetus, heavy cigarette smokers, and alcohol and drug abusers). 23 Taking excessive amounts of a multivitamin and mineral supplement may be harmful to the mother and/or fetus and should be avoided.
Pregnant women who are strict vegetarians (vegan-vegetarians) may need vitamin B 12 supplementation. 23

Recommended intakes for all vitamins and most minerals are increased during breast-feeding. 2

Recommended intakes may be increased by the following medications: Aminosalicylates, 1 colchicine, 1 and epoetin 30.

Vitamin B 12 should not be administered as a dietary supplement before pernicious anemia or folic acid deficiency has been ruled out. 4

[Vitamin B 12 deficiency (diagnosis)]¾Cyanocobalamin or hydroxocobalamin may be used as the flushing dose in the Schilling test for vitamin B 12 malabsorption. 1, 25

Unaccepted 7

Cyanocobalamin has not been proven effective for treatment of acute viral hepatitis; aging; allergies; amblyopia; delayed growth, poor appetite, 26 or malnutrition; dermatologic disorders; fatigue 4 ; mental disorders 4, 26 ; multiple sclerosis; sterility; thyrotoxicosis; and trigeminal neuralgia and other neuropathies. 4

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾Cyanocobalamin: 1355.39 20

Hydroxocobalamin: 1346.38 20

Mechanism of action/Effect:

Vitamin B 12 acts as a coenzyme for various metabolic functions, including fat 3 and carbohydrate metabolism 4 and protein synthesis. It is necessary for growth, cell replication, hematopoiesis, 4 and nucleoprotein 3, 4 and myelin synthesis, 1, 4 largely due to its effects on metabolism of methionine 2, 4 , folic acid, and malonic acid.

Absorption:

The B vitamins are readily absorbed from the gastrointestinal tract, except in malabsorption syndromes. Vitamin B 12 is absorbed in the lower half of the ileum. 2

Dietary vitamin B 12 is released from the proteins to which it is bound by gastric acid and pancreatic proteases, before being bound to the intrinsic factor (IF).
A vitamin B 12-IF complex is formed and passes down the intestine where it binds with receptor sites on the ileal mucosa so that vitamin B 12 can be absorbed into the systemic circulation. 4, 27 Calcium and a pH greater than 5.4 are required for attachment to the receptor sites. 3, 7, 27

The enterohepatic circulation conserves vitamin B 12 by reabsorbing vitamin B 12 from bile. 2, 4, 5, 11, 12

Protein binding:

2, 4 Very high (to specific plasma proteins called transcobalamins); binding of hydroxocobalamin is slightly higher than cyanocobalamin.

Storage

Hepatic (90%); some renal. 1

Biotransformation:

Hepatic. 2

Half-life:

Approximately 6 days (400 days in the liver).

Time to peak plasma concentration

After oral administration¾8 to 12 hours.
After intramuscular administration¾60 minutes.

Elimination:

Biliary. Excess beyond daily needs is excreted, largely unchanged, in urine.

Precautions to Consider

Cross-sensitivity and/or related problems

Individuals sensitive to other cobalamins (found naturally in foods) may be sensitive to vitamin B 12 also.

Carcinogenicity

Studies have not been done in either animals or humans. 1

Pregnancy/Reproduction

Pregnancy¾Studies have not been done in humans. 1 Problems in humans have not been documented with intake of normal daily recommended amounts.
Studies have not been done in animals.
FDA Pregnancy Category C (nasal and parenteral). 1, 49

Breast-feeding

Vitamin B 12 is distributed into breast milk; 8 however, problems in humans have not been documented with intake of normal daily recommended amounts.

Pediatrics

Problems in pediatrics have not been documented with intake of normal daily recommended amounts.
Cyanocobalamin injection that contains benzyl alcohol as a preservative should not be used in newborn and immature infants. The use of benzyl alcohol in neonates has been associated with a fatal toxic syndrome consisting of metabolic acidosis and central nervous system (CNS), respiratory, circulatory, and renal function impairment. 9, 10

Geriatrics

Problems in geriatrics have not been documented with intake of normal daily recommended amounts.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following, depending on the amount present, may also interact with vitamin B 12 supplements.
Alcohol, excessive intake for longer than 2 weeks 1, 28 or

Aminosalicylates or 1

Colchicine, 1, 24, 27 especially in combination with aminoglycosides

(may act to reduce absorption of vitamin B 12 from the gastrointestinal tract; requirements for vitamin B 12 may be increased in patients receiving these medications)

Antibiotics

(may interfere with the microbiologic method of assay for serum and erythrocyte vitamin B 12 concentrations and cause falsely low results 1, 7)

Folic acid

(large and continuous doses may reduce vitamin B 12 concentrations in blood)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

For cyanocobalamin

>> Leber''s disease

(optic nerve atrophy has occurred rapidly after administration; cyanocobalamin concentrations are already elevated 1)

Risk-benefit should be considered when the following medical problem exists

Sensitivity to cyanocobalamin or hydroxocobalamin

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Folic acid concentrations, plasma and 1, 49

Hematocrit and 1, 49

Platelet and 49

Reticulocyte count, plasma and 1, 49

Vitamin B 12 concentrations, plasma 1, 49

(determinations recommended prior to treatment and between the 5th and 7th days of therapy; for nasal dosage form, these measurements are recommended initially at 1 month after the start of treatment and at intervals of 3 to 6 months thereafter 49)

Potassium concentrations, serum 1, 49

(determinations recommended during first 48 hours of treatment of megaloblastic anemia to detect possible serious hypokalemia, which could result in sudden death 1)

Side/Adverse Effects

Note: Water-soluble vitamins seldom cause toxicity in persons with normal renal function. 1

Treatment with vitamin B 12 may unmask the signs of polycythemia vera. 1

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Anaphylactic reaction (skin rash; itching; wheezing)¾after parenteral administration
Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent

Diarrhea 1; itching of skin 1

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Vitamin B 12 (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Description of use

Description should include function in the body, signs of deficiency, and unproven uses

Importance of diet

Importance of proper nutrition; supplement may be needed because of inadequate dietary intake

Food sources of vitamin B 12; effects of processing

Not using vitamins as substitute for balanced diet

Recommended daily intake for vitamin B 12

Before using this dietary supplement

>> Conditions affecting use, especially:

Sensitivity to cobalamins
Other medical problems, especially Leber"s disease
Proper use of this dietary supplement

>> Taking at least one hour before or one hour after hot foods or liquids

>> Importance of follow-up blood tests every 3 to 6 months

>> Proper dosing
>> Need for lifelong therapy for pernicious anemia or following gastrectomy or ileal resection

Missed dose: No cause for concern because of length of time necessary for depletion; remembering to take as directed
>> Proper storage
Side/adverse effects

Signs of potential side effects, especially anaphylactic reaction

General Dosing Information

Because of the infrequency of single B vitamin deficiencies, combinations are commonly administered. Many commercial combinations of B vitamins are available.
Vitamin B 12 is also synthesized by bacteria in the gastrointestinal tract but is not absorbed and is excreted in the feces. 2

A diagnosis of vitamin B 12 deficiency should be confirmed by laboratory investigations before institution of vitamin B 12 therapy; vitamin B 12 administration may mask folic acid deficiency. 4

For nasal dosage form only

Cyanocobalamin USP intranasal gel is administered in patients with vitamin B12 malabsorption who are in remission following injectable vitamin B12 therapy 49.

For oral dosage forms only

The oral route is useful only for treating nutritional vitamin B 12 deficiency (when gastrointestinal absorption is normal or in vegan-vegetarians); it is not useful in small bowel disease, malabsorption syndromes, or following gastric or ileal resection. Oral preparations containing intrinsic factor have little reliable continuous efficacy in pernicious anemia. 4

For parenteral dosage forms only

Cyanocobalamin or hydroxocobalamin injection should not be administered intravenously, 1 although small amounts of cyanocobalamin are sometimes included in total parenteral nutrition (TPN) solutions.

Diet/Nutrition

Recommended dietary intakes for vitamin B 12 are defined differently worldwide.

For U.S.¾
The Recommended Dietary Allowances (RDAs) for vitamins and minerals are determined by the Food and Nutrition Board of the National Research Council and are intended to provide adequate nutrition in most healthy persons under usual environmental stresses. In addition, a different designation may be used by the FDA for food and dietary supplement labeling purposes, as with Daily Value (DV). DVs replace the previous labeling terminology United States Recommended Daily Allowances (USRDAs). 2, 33

For Canada¾ Recommended Nutrient Intakes (RNIs) for vitamins, minerals, and protein are determined by Health and Welfare Canada and provide recommended amounts of a specific nutrient while minimizing the risk of chronic diseases. 35

Daily recommended intakes for vitamin B 12 are generally defined as follows: 2, 33

Persons	U.S. (mcg)	Canada (mcg)

Infants and children	0.3-0.7	0.3-0.4
Birth to 3 years of age		
4 to 6 years of age	1	0.5
7 to 10 years of age	1.4	0.8-1
Adolescent and adult males	2	1-2
Adolescent and adult females	2	1-2
Pregnant females	2.2	2-3
Breast-feeding females	2.6	1.5-2.5

These are usually provided by adequate diets.

Best dietary sources of vitamin B 12 are fish, seafood, 3 egg yolk, milk, and fermented cheeses. Vitamin B 12 is not found in vegetables; 1 however, bacteria found on vegetables may be a source of vitamin B 12 for vegan-vegetarians. 2, 4 There is little loss of vitamin B 12 from foods with ordinary cooking; however, severe heating may cause degeneration. 3

CYANOCOBALAMIN

Summary of Differences

Indications for cyanocobalamin and hydroxocobalamin are the same, although hydroxocobalamin may be preferred for treatment of vitamin B 12 deficiency since optic neuropathies may degenerate with administration of cyanocobalamin. 1 However, some patients develop antibodies to the hydroxocobalamin-transcobalamin II complex. 6 Cyanocobalamin USP intranasal gel is administered in patients who are in hematologic remission following injectable vitamin B12 therapy 49.

Nasal Dosage Form

CYANOCOBALAMIN INTRANASAL GEL USP

Usual adult

Deficiency (prophylaxis)¾
Intranasal, 500 mcg (0.5 mg) once a week. The dosage may be increased based on the serum levels of vitamin B12 49.

Note: If the serum levels of vitamin B12 are low continuously during the therapy, this mode of administration may not be indicated for the patient 49.

Usual pediatric dose

Deficiency (prophylaxis)¾
Intranasal, amount based on normal daily recommended intakes
Strength(s) usually available¾U.S.¾500 mcg (0.5 mg) per actuation (0.1 mL per actuation) (Rx)[NascobalÒ (methylcellulose) (sodium citrate) (citric acid) (glycerin) (benzylkonium chloride)]

Note: Cyanocobalamin gel for intranasal administration is available as a metered dose gel in 5-mL glass bottles containing 2.3 mL of gel 49.

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing 49.

Auxiliary labeling:

· Take at least one hour before or one hour after hot foods or liquids.
· Keep upright and covered in prescription vial until ready to use.

Oral Dosage Forms

CYANOCOBALAMIN TABLETS

Usual adult and adolescent dose

Deficiency (prophylaxis)¾
Oral, amount based on normal daily recommended intakes: 2, 33

Persons	U.S. (mcg)	Canada (mcg)
Adolescent and adult males	2	1-2
Adolescent and adult females	2	1-2
Pregnant females	2.2	2-3
Breast-feeding females	2.6	1.5-2.5

Deficiency (treatment)¾
Treatment dose is individualized by prescriber based on severity of deficiency.

Usual pediatric dose

Deficiency (prophylaxis)¾
Oral, amount based on normal daily recommended intakes: 2, 33

Persons	U.S.	Canada

	(mcg)	(mcg)
Infants and children	0.3-0.7	0.3-0.4
Birth to 3 years of age		
4 to 6 years of age	1	0.5
7 to 10 years of age	1.4	0.8-1

Deficiency (treatment)¾
Treatment dose is individualized by prescriber based on severity of deficiency.

Strength(s) usually available

U.S.¾25 mcg (0.025 mg) (OTC) [Generic]

50 mcg (0.05 mg) (OTC) [Generic]

100 mcg (0.1 mg) (OTC) [Generic]

200 mcg (0.2 mg) (OTC) [Generic] 37

250 mcg (0.25 mg) (OTC) [Generic]

500 mcg (0.5 mg) (OTC) [Generic]

1000 mcg (1 mg) (OTC) [Generic]

1500 mcg (1.5 mg) (OTC) [Generic] 37, 38

Canada¾10 mcg (0.01 mg) (OTC) [Generic]

25 mcg (0.025 mg) (OTC) [Generic]

100 mcg (0.1 mg) (OTC) [Generic]

250 mcg (0.25 mg) (OTC) [Generic]

Note: Some strengths of these cyanocobalamin preparations may exceed the dosage range recommended by USP DI Advisory Panels based on the amount necessary to meet normal nutritional needs.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light.

CYANOCOBALAMIN EXTENDED-RELEASE TABLETS

Usual adult and adolescent dose

See Cyanocobalamin Tablets.

Usual pediatric dose

Dosage form not suitable for use in children.

Strength(s) usually available

U.S.¾100 mcg (0.1 mg) (OTC) [Generic] 37

200 mcg (0.2 mg) (OTC) [Generic] 37

500 mcg (0.5 mg) (OTC) [Generic] 37

1000 mcg (1 mg) (OTC) [Generic] 37

Canada¾Not commercially available.

Note: Some strengths of these cyanocobalamin preparations may exceed the dosage range recommended by USP DI Advisory Panels based on the amount necessary to meet normal nutritional needs.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from light.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

CYANOCOBALAMIN INJECTION USP

Usual and adolescent adult dose

Deficiency (prophylaxis)¾
Intravenous infusion, as part of total parenteral nutrition solutions, the specific amount determined by individual patient need.
Deficiency (treatment)¾
Initial: Intramuscular or deep subcutaneous, 100 mcg (0.1 mg) per day for six or seven days, followed by 100 mcg (0.1 mg) every other day for seven doses if clinical improvement and a reticulocyte response occur, then 100 mcg (0.1 mg) every three or four days for another two to three weeks. 1

Maintenance: Intramuscular, 100 to 200 mcg (0.1 to 0.2 mg) once a month (in pernicious anemia and following total gastrectomy and extensive ileal resection, parenteral maintenance supplementation is continued for life). 1

[Diagnostic aid (vitamin B 12 deficiency)]¾
Intramuscular, 1 mcg (0.001 mg) per day for ten days plus low dietary folic acid and vitamin B 12. The flushing dose for the Schilling test is 1000 mcg (1 mg) intramuscularly. 1, 25

Usual pediatric dose

Deficiency (prophylaxis)¾
Intravenous infusion, as part of total parenteral nutrition solutions, the specific amount determined by individual patient need.
Deficiency (treatment)¾
Initial: Intramuscular or deep subcutaneous, 30 to 50 mcg (0.03 to 0.05 mg) per day for two or more weeks (total dose of 1 to 5 mg). 13, 14

Maintenance: Intramuscular or deep subcutaneous, 100 mcg (0.1 mg) once a month as necessary (for life in the case of pernicious anemia and following total gastrectomy and extensive ileal resection). 13

Note: Cyanocobalamin injection that contains benzyl alcohol as a preservative should not be used in newborn and immature infants. The use of benzyl alcohol in neonates has been associated with a fatal toxic syndrome consisting of metabolic acidosis and CNS, respiratory, circulatory, and renal function impairment.

Strength(s) usually available

U.S.¾30 mcg (0.03 mg) per mL (Rx) [Generic]

100 mcg (0.1 mg) per mL (Rx)[Rubramin PC (benzyl alcohol)] [Generic]

1000 mcg (1 mg) per mL (Rx)[Cobex] [Cobolin-M 42] [Crystamine] [Crysti-12] [Cyanoject (benzyl alcohol)] [Cyomin (benzyl alcohol)] [Neuroforte-R 43] [Primabalt 44] [Rubramin PC (benzyl alcohol)] [Shovite 45] [Vibal 46] [Vitabee 12 41] [Generic]

Canada¾100 mcg (0.1 mg) per mL (Rx) [Generic] 36

1000 mcg (1 mg) per mL (Rx)[Anacobin 40] [40 Bedoz] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a light-resistant container. Protect from freezing.

Incompatibilities:

Cyanocobalamin injection is physically incompatible with warfarin sodium for injection.

HYDROXOCOBALAMIN

Summary of Differences

Indications for cyanocobalamin and hydroxocobalamin are the same, although hydroxocobalamin may be preferred for treatment of vitamin B 12 deficiency since optic neuropathies may degenerate with administration of cyanocobalamin. 1 However, some patients develop antibodies to the hydroxocobalamin-transcobalamin II complex. 6

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

HYDROXOCOBALAMIN INJECTION USP

Usual adult and adolescent dose

Deficiency (prophylaxis)¾
Intravenous infusion, as part of total parenteral nutrition solutions, the specific amount determined by individual patient need.
Deficiency (treatment)¾
Initial: Intramuscular or deep subcutaneous, 30 to 50 mcg (0.03 to 0.05 mg) per day (100 mcg [0.1 mg] if megaloblastic anemia is severe) for five to ten days.
Maintenance: Intramuscular, 100 to 200 mcg (0.1 to 0.2 mg) once a month (in pernicious anemia and following total gastrectomy and extensive ileal resection, parenteral maintenance supplementation is continued for life).
[Diagnostic aid (vitamin B 12 deficiency)]¾
Intramuscular, 1 mcg (0.001 mg) per day for ten days plus low dietary folic acid and vitamin B 12. The flushing dose for the Schilling test is 1000 mcg (1 mg) intramuscularly. 25

Usual pediatric dose

Deficiency (prophylaxis)¾
Intravenous infusion, as part of total parenteral nutrition solutions, the specific amount determined by individual patient need.
Deficiency (treatment)¾
Initial: Intramuscular or deep subcutaneous, 30 to 50 mcg (0.03 to 0.05 mg) per day for two or more weeks (total dose of 1 to 5 mg).
Maintenance: Intramuscular or deep subcutaneous, 100 mcg (0.1 mg) once a month as necessary (for life in the case of pernicious anemia and following total gastrectomy and extensive ileal resection).

Strength(s) usually available

U.S.¾100 mcg (0.1 mg) per mL (Rx)[Alphamin] [Generic] 47

1000 mcg (1 mg) per mL (Rx)[Alphamin] [Hydrobexan] [Hydro-Cobex] [Hydro-Crysti-12] [Hydroxy-Cobal 47] [LA-12] [Vibal LA 46] [Generic]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.