

# Vitamin B12

**Class:** Vitamin B Complex

**VA Class:** VT100

**Chemical Name:** 5,6-dimethyl-benzimidazolyl cyanocobamide,

**CAS Number:** 68-19-9

**Brands:** Nascobal

## Introduction

A cobalt-containing, B complex vitamin. Cyanocobalamin and hydroxocobalamin are synthetic forms of vitamin B<sub>12</sub>.

Hydroxocobalamin: Antidote for cyanide poisoning.

## Uses for Vitamin B12

### Vitamin B12 Deficiency

Treatment of pernicious anemia and other vitamin B<sub>12</sub> deficiency states.

Parenteral cyanocobalamin or hydroxocobalamin: Treatment of vitamin B<sub>12</sub> deficiency due to inadequate intrinsic factor (IF) secretion; impaired intestinal absorption; or dietary deficiency associated with a vegetarian diet.

Cyanocobalamin is considered the parenteral vitamin B<sub>12</sub> preparation of choice; hydroxocobalamin may be preferred for initial treatment.

Cyanocobalamin nasal spray: Used to maintain hematologic status in adults with pernicious anemia with no nervous system involvement who have responded to parenteral vitamin B<sub>12</sub> therapy. Also used as a supplement for vitamin B<sub>12</sub> deficiency due to dietary deficiency, impaired absorption, inadequate secretion of IF, or certain other conditions.

### Dietary Requirements

Adequate intake needed to prevent vitamin B<sub>12</sub> deficiency and neurologic complications associated with vitamin B<sub>12</sub> deficiency.

Adequate intake of vitamin B<sub>12</sub> usually can be accomplished through consumption of foodstuffs; however, about 10–30% of geriatric individuals are unable to absorb naturally occurring vitamin B<sub>12</sub> and should consume vitamin B<sub>12</sub>-fortified food or supplements. Inadequate intake can occur in

vegetarians and their breast-fed infants. Mixed foods whose main ingredient is meat, fish, or poultry; milk; and fortified ready-to-eat cereals are the main sources of vitamin B<sub>12</sub> in the diet of US adults and children.

Recommended Dietary Allowance (RDA) in adults based on amount needed to maintain hematologic status and normal serum vitamin B<sub>12</sub> concentrations.

Adequate intake (AI) established for infants ≤6 months of age based on observed mean vitamin B<sub>12</sub> intake of infants fed principally human milk; AI for infants 7–12 months of age based on AI for younger infants and data in adults.

RDA for children 1–18 years of age based on data in adults.

## **Metabolic Disorders**

Parenteral cyanocobalamin: Management of hereditary deficiency of transcobalamin II.

## **Schilling Test**

Parenteral cyanocobalamin and hydroxocobalamin: Used in conjunction with cyanocobalamin Co 57 in Schilling test to study vitamin B<sub>12</sub> absorption.

## **Cyanide Poisoning**

Hydroxocobalamin (Cyanokit): Treatment of known or suspected cyanide poisoning. Used in conjunction with airway and cardiovascular support and management of seizure activity.

## **Vitamin B12 Dosage and Administration**

### **Administration**

Cyanocobalamin is administered orally, intranasally, or by IM or deep sub-Q injection.

Hydroxocobalamin is administered by IM injection or IV infusion.

### **Oral Administration**

Oral therapy is inferior to parenteral therapy. May be used for treatment of dietary vitamin B<sub>12</sub> deficiency in patients with normal GI absorption.

### **Parenteral Administration**

Cyanocobalamin: Administer by IM or deep sub-Q injection. If administered sub-Q, avoid injection into the dermis or upper subcutaneous tissue. Avoid administering IV; vitamin is rapidly excreted in urine when administered IV.

Hydroxocobalamin: Administer by IM injection (vitamin deficiency) or by IV infusion (cyanide poisoning). Avoid administering IV for vitamin deficiency.

For drug compatibility information, see Compatibility under Stability.

#### **IV Administration for Cyanide Poisoning**

Hydroxocobalamin: (Cyanokit); Administer by IV infusion.

May require a dedicated IV line. Administration through the same IV line as blood products not recommended.

#### **Reconstitution**

Reconstitute vial containing 2.5 g of hydroxocobalamin with 100 mL of 0.9% sodium chloride injection; invert or rock vial for at least 30 seconds. Do *not* shake vial. Lactated Ringer's injection or 5% dextrose injection can be used if 0.9% sodium chloride injection is not available. Reconstituted solution contains 25 mg/mL.

#### **Rate of Administration**

Initial 5-g dose: 15 minutes.

Second 5-g dose: 15 minutes (for patients in extremis) to 2 hours; rate depends on patient condition.

#### **Intranasal Administration**

Administer intranasally using a metered-dose pump. Administer 1 hour before or 1 hour after ingestion of hot foods or liquids.

Prior to intranasal administration, clear nasal passages. Insert the nasal adapter 1 cm into one nostril, point the tip of the adapter toward the back of the nose, hold the other nostril closed, and tilt head slightly forward, pump the drug into nostril, sniff gently during and immediately after dosing, return head to upright position, remove pump unit from nose.

Efficacy has not been established in patients with nasal congestion, allergic rhinitis, or upper respiratory tract infection; defer use until these symptoms have subsided.

Prime the pump before each use.

#### **Dosage**

Vitamin B<sub>12</sub> deficiency: Duration of therapy depends on cause; long-term therapy not needed when other therapeutic measures correct the underlying cause of the deficiency.

Cyanocobalamin metered-dose pump delivers 500 mcg of the drug (0.1 mL) per actuation.

## **Pediatric Patients**

### **Vitamin B 12 Deficiency**

#### **IM**

Hydroxocobalamin: Initially, single doses of 100 mcg to total dose of 1–5 mg given over  $\geq 2$  weeks.

Hydroxocobalamin: Maintenance, 30–50 mcg every 4 weeks.

### **Dietary and Replacement Requirements**

#### **Oral**

Infants born to vegan mothers: Supplement with AI from birth because these infants' vitamin B<sub>12</sub> stores are low and their mother's milk may supply very small amounts of the vitamin.

Infants  $\leq 6$  months of age: Recommended AI is 0.4 mcg (0.06 mcg/kg) daily.

Infants 7–12 months of age: Recommended AI is 0.5 mcg (0.06 mcg/kg) daily.

Children 1–3 years of age: RDA is 0.9 mcg daily.

Children 4–8 years of age: RDA is 1.2 mcg daily.

Children 9–13 years of age: RDA is 1.8 mcg daily.

Children 14–18 years of age: RDA is 2.4 mcg daily.

The RDAs will not meet the needs of individuals with malabsorption syndrome.

### **Cyanide Poisoning†**

#### **IV**

Hydroxocobalamin: 70 mg/kg has been used.

## **Adults**

### **Vitamin B 12 Deficiency**

#### **IM or Sub-Q**

Cyanocobalamin: Initially, 100 mcg daily for 6–7 days. If clinical manifestations improve and reticulocyte response observed, administer 100 mcg every other day for 7 doses and then 100 mcg every 3–4 days for 2–3 weeks.

Cyanocobalamin: Maintenance, 100 mcg every month.

#### **IM**

Hydroxocobalamin: Initially, 30 mcg daily for 5–10 days.

Hydroxocobalamin: Maintenance, 100–200 mcg every month.

### **Intranasal**

Maintenance, 500 mcg (one actuation) once weekly. Increase dose in patients who experience a decline in serum vitamin B<sub>12</sub> concentrations after 1 month of therapy.

### **Dietary and Replacement Requirements**

#### **Oral**

Men and women ≥19 years of age: RDA is 2.4 mcg daily.

Adults ≥51 years of age should obtain most of their vitamin B<sub>12</sub> from fortified food or a vitamin B<sub>12</sub> supplement.

The RDAs will not meet the needs of individuals with malabsorption syndrome.

### **Cyanide Poisoning**

#### **IV**

Hydroxocobalamin: Initially, 5 g (two 2.5-g vials). A second 5-g dose may be administered, based on the severity of the poisoning and clinical response.

#### **Schilling Test**

#### **IM or Sub-Q**

Cyanocobalamin: Flushing dose is 1000 mcg.

#### **IM**

Hydroxocobalamin: Flushing dose is 1000 mcg.

### **Special Populations**

#### **Pregnant Women**

RDA for pregnant women is 2.6 mcg daily.

#### **Lactating Women**

RDA for lactating women is 2.8 mcg daily.

Requirements increased in lactating women to ensure adequate concentration of the vitamin in milk.

## **Cautions for Vitamin B12**

### **Contraindications**

- Known hypersensitivity to vitamin B<sub>12</sub>, cobalt, or any ingredient in the formulation.

- No contraindications when used for treatment of cyanide poisoning.

## **Warnings/Precautions**

### **Warnings**

#### **Hypokalemia**

Fatal hypokalemia reported in intensively treated patients with megaloblastic anemia. Monitor serum potassium concentrations during early vitamin B<sub>12</sub> therapy and administer potassium if necessary.

#### **Polycythemia Vera**

Vitamin B<sub>12</sub> deficiency may suppress signs of polycythemia vera; treatment may unmask this condition.

#### **Ocular Effects**

Avoid use in patients with early Leber's disease (hereditary optic nerve atrophy); rapid and severe optic nerve atrophy reported.

### **Sensitivity Reactions**

#### **Sensitivity Reactions**

Anaphylaxis reported with parenteral preparations.

Hydroxocobalamin (Cyanokit): Rash, mainly acneiform, reported in 20 or 44% of individuals receiving a 5- or 10-g dose, respectively.

#### **Skin Test**

Administer an intradermal test dose prior to administration of vitamin B<sub>12</sub> for vitamin deficiency in patients who may be sensitive to cobalamins.

### **General Precautions**

#### **Laboratory Monitoring**

Obtain hematocrit, reticulocyte count, vitamin B<sub>12</sub>, folate, and iron levels prior to treatment for vitamin B<sub>12</sub> deficiency. Monitor hematologic parameters as necessary during therapy.

#### **Aluminum**

Some cyanocobalamin injection preparations contain aluminum, which may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum >4–5 mcg/kg daily accumulate aluminum at levels associated

with CNS and bone toxicity. Tissue loading may occur at even lower rates of administration.

### **Benzyl Alcohol in Neonates**

Cyanocobalamin injection may contain benzyl alcohol as a preservative; benzyl alcohol has been associated with toxicity in neonates. (See Pediatric Precautions.)

### **Blood Pressure**

Transient elevations in BP reported in individuals receiving IV hydroxocobalamin.

### **Undiagnosed Anemia**

Use extreme caution if folic acid is administered to patients with undiagnosed anemia; may obscure the diagnosis of pernicious anemia by alleviating hematologic manifestations of the disease while allowing neurologic complications to progress.

### **Renal Effects**

Oxalate crystals observed in the urine of healthy individuals and cyanide poisoning victims following administration of hydroxocobalamin.

## **Specific Populations**

### **Pregnancy**

Category C.

### **Lactation**

Distributed into human milk.

Hydroxocobalamin (Cyanokit): Caution advised; no data available to determine when breast-feeding may be restarted following administration of IV hydroxocobalamin.

### **Pediatric Use**

Hydroxocobalamin (Cyanokit): Safety and efficacy not established.

Cyanocobalamin: Benzyl alcohol has been associated with toxicity (“gasping syndrome”) in neonates; each mL of cyanocobalamin injection (e.g., preparation manufactured by Abraxis) contains 15 mg of benzyl alcohol.

### **Geriatric Use**

Hydroxocobalamin (Cyanokit): No substantial differences in safety and efficacy relative to younger adults. Dosage adjustment not needed.

### **Hepatic Impairment**

Hydroxocobalamin (Cyanokit): Safety and efficacy not studied in patients with hepatic impairment.

### **Renal Impairment**

Hydroxocobalamin (Cyanokit): Safety and efficacy not studied in patients with renal impairment. Hydroxocobalamin and cyanocobalamin excreted unchanged in urine.

## Common Adverse Effects

Usually nontoxic even in large doses; mild transient diarrhea, peripheral vascular thrombosis, itching, transitory exanthema, urticaria, body swelling reported in patients receiving parenteral preparations.

## Interactions for Vitamin B<sub>12</sub>

Colchicine, aminosalicic acid and its salts, and excessive alcohol intake lasting >2 weeks may reduce absorption of vitamin B<sub>12</sub> from the GI tract.

## Specific Drugs and Laboratory Tests

Drug	Interaction	Comments
Ascorbic acid	May destroy substantial amounts of dietary vitamin B <sub>12</sub>	Consider this if large doses of ascorbic acid are ingested within 1 hour of administration of oral vitamin B <sub>12</sub>
Chloramphenicol	May antagonize the hematopoietic response to vitamin B <sub>12</sub> in vitamin-deficient patients	Monitor; consider alternate anti-infectives
Cyanide antidotes	Safety of concomitant use of hydroxocobalamin with other cyanide antidotes not established	Caution (See Parenteral under Stability and IV Administration under Dosage and Administration)
Laboratory parameters determined by colorimetric methods	Hydroxocobalamin (Cyanokit): Deep red color in blood and/or urine may interfere with certain laboratory tests (e.g., clinical chemistry, hematology, coagulation, urine parameters)	Consult the product labeling for specific information
Methotrexate	Invalidates diagnostic microbiologic blood assays for vitamin B <sub>12</sub>	
Prednisone	Increased absorption of vitamin B <sub>12</sub> and secretion of IF reported in a few patients with	Does not occur in patients with partial or total



	pernicious anemia	gastrectomy; clinical importance unknown
Pyrimethamine	Invalidates diagnostic microbiologic blood assays for vitamin B <sub>12</sub>	
Test for intrinsic factor (IF) antibodies	Prior administration of cyanocobalamin may result in false-positive test results	

## Vitamin B12 Pharmacokinetics

### Absorption

#### Bioavailability

Irregularly absorbed from the distal small intestine following oral administration. Requires gastric IF for active absorption from the GI tract.

Following parenteral (IM or sub-Q) administration, hydroxocobalamin is absorbed more slowly than cyanocobalamin.

Following administration of cyanocobalamin nasal spray, bioavailability is about 6.1% compared with IM administration.

### Distribution

#### Extent

Distributed into liver, bone marrow, and other tissues.

Crosses the placenta and is distributed into milk.

### Elimination

#### Elimination Route

50–98% may be excreted in urine.

### Stability

### Storage

#### Oral

##### Tablets

Cool dry place.

## Parenteral

### Solution for Injection

20–25°C; protect from light.

### Powder for Injection

25°C (may be exposed to 15–30°C). May be stored for short periods at temperatures that occur with usual transport (15 days 5–40°C), transport in the desert (4 days 5–60°C), and freeze/defrost cycles (15 days in a range from –20 to 40°C).

Store reconstituted solution at ≤40°C; discard 6 hours after reconstitution.

## Nasal Spray

Upright at 15–30°C; protect from light. Keep covered in carton until needed. Protect from freezing.

## Compatibility

For information on systemic interactions resulting from concomitant use, see Interactions.

## Parenteral

Hydroxocobalamin (Cyanokit): Incompatible with ascorbic acid, diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, pentobarbital, propofol, sodium nitrite, sodium thiosulfate, thiopental.

Cyanocobalamin injection: Reported to be incompatible with chlorpromazine hydrochloride, phytonadione, prochlorperazine edisylate, warfarin sodium, ascorbic acid, dextrose, heavy metals, oxidizing or reducing agents, and alkaline or strongly acidic solutions.

### Cyanocobalamin: Solution Compatibility

Compatible
Dextran 6% in dextrose 5%
Dextran 6% in sodium chloride 0.9%
Dextrose-Ringer's injection combinations
Dextrose-Ringer's injection, lactated, combinations
Dextrose-saline combinations
Dextrose 2½, 5, or 10% in water

Fructose 10% in sodium chloride 0.9%
Fructose 10% in water
Invert sugar 5 and 10% in sodium chloride 0.9%
Invert sugar 5 and 10% in water
Ionosol products
Ringer's injection
Ringer's injection, lactated
Sodium chloride 0.45 or 0.9%
Sodium lactate 1/6 M

#### Cyanocobalamin: Drug Compatibility

Admixture CompatibilityHID
<b>Compatible</b>
Ascorbic acid injection
Chloramphenicol sodium phosphate
Metaraminol bitartrate
Vitamin B complex with C

Y-Site CompatibilityHID
<b>Compatible</b>
Heparin sodium
Hydrocortisone sodium succinate
Potassium chloride
Vitamin B complex with C

## Actions

- An exogenous source of vitamin B<sub>12</sub> is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and the maintenance of normal erythropoiesis.
- In cyanide poisoning, hydroxocobalamin binds to the cyanide ion to form cyanocobalamin which is excreted in the urine.

## Advice to Patients

- Advise patients with pernicious anemia that they must receive maintenance dosages of cyanocobalamin or hydroxocobalamin for the remainder of their lives to prevent irreversible neurologic damage.
- Advise patient of necessity of follow-up tests to confirm adequacy of therapy.
- Advise individuals who follow a vegetarian diet that contains no animal products to take oral vitamin B<sub>12</sub> regularly.
- Importance of informing patients using intranasal cyanocobalamin to administer the dose at least 1 hour before or after ingestion of hot foods or liquids.
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.
- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of vitamin B<sub>12</sub> supplements in pregnant and lactating women who follow a vegetarian diet. Advise women given hydroxocobalamin for cyanide poisoning to discuss timing of resumption of breast-feeding with their clinician.
- Advise patients given hydroxocobalamin for cyanide poisoning that skin redness may last up to 2 weeks and urine coloration may last up to 5 weeks. Importance of avoiding direct sun exposure while skin is discolored.
- Importance of informing patients of other important precautionary information. (See Cautions.)

## Preparations

*Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.*

*Please refer to the ASHP Drug Shortages Resource Center for information on shortages of one or more of these preparations.*

\* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Cyanocobalamin				
Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Oral	Tablets	25 mcg*		
		50 mcg*		
		100 mcg*		
		250 mcg*		
		500 mcg*		
		1000 mcg*		
Parenteral	Injection	100 mcg/mL*		
		1000 mcg/mL*		
Nasal	Spray	500 mcg/metered spray	Nascobal (with benzalkonium chloride)	QOL Medical

\* available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Hydroxocobalamin				
Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Parenteral	Injection	1000 mcg/mL*		
	For Injection	2.5 g	Cyanokit	Dey

Vitamin B<sub>12</sub> is also commercially available in combination with other vitamins and minerals.

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† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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