February 6, 2025

IMPORTANT DRUG INFORMATION

Subject: Infusion set with 0.2 micron in-line filter having a membrane surface greater than or equal to 10 cm^2 to be temporarily used for administration of CYANOKIT® (hydroxocobalamin for injection) 5 g powder for intravenous infusion to prevent potential microbial infection

Dear Healthcare Professional,

The purpose of this letter is to inform you of important information concerning Cyanokit (hydroxocobalamin for injection). The manufacturing of Cyanokit has been suspended due to the investigation of an ongoing quality defect resulting in the potential for Cyanokit to not be sterile. This has resulted in a shortage of the product in the United States. To address the current drug shortage, BTG International Inc (a SERB Pharmaceuticals company) is coordinating with the U.S. Food and Drug Administration (FDA) to make the following impacted batches available to U.S. patients during this period of shortage.

NDC	Description	Batch Number	Expiry date
50633-310-11	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2207	4/7/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2210	6/1/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2208	5/15/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2211	6/8/2025

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BTG International Inc is now a **SERB Pharmaceuticals** *company*

	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2213	6/27/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2216	9/26/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2220	11/7/2025
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2301	1/3/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2302	1/10/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2304	1/24/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2307	3/21/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2311	5/2/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2313	5/23/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2316	6/14/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2319	9/27/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2322	10/30/2026

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	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2317	8/28/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2325	11/20/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2324	11/14/2026
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2402	1/11/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2405	1/31/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2407	2/15/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2410	04/10/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2414	5/30/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2415	06/05/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2416	6/13/2027
	CYANOKIT (hydroxocobalamin for injection) 5 g powder for intravenous infusion	2418	6/26/2027

Description of the Quality Defect:

The quality defect involves a potential risk of microbial contamination that would compromise the product's sterility and lead to a potential risk of systemic infection or sepsis in patients

receiving Cyanokit.

All currently available batches of Cyanokit (as listed in the above table) are potentially affected by this quality defect (microbial contamination).

Although these batches met required specifications for release, including sterility and endotoxin, SERB Pharmaceuticals is unable to assure their sterility or endotoxin content.

Risks Associated with Use of the Impacted Product:

SERB Pharmaceuticals conducted a risk assessment, which demonstrates that it is not possible to eliminate all sterility assurance risks for the affected batches. The risk of microbial contamination in these batches cannot be totally excluded. Healthcare providers should weigh the potential benefit of using Cyanokit against the potential risk of infection.

The decision was reached as the risk to patients from non-availability of Cyanokit, which is considered critical, is considered a greater risk to public health than the risk associated with making these batches available and healthcare providers taking appropriate precautions upon administration.

No safety signals related to this quality defect have been reported at this stage. SERB Pharmaceuticals will continue to monitor the risk through pharmacovigilance data including adverse event reporting, customer complaint and medical information processes.

Recommended Actions:

- Healthcare professionals likely to use these impacted batches (as listed above) should ensure that:
    - Patients who receive Cyanokit should be closely monitored for signs of systemic infection or sepsis. If systemic infection or sepsis is suspected (e.g., fever, persistent hypotension indicative of shock), initiate blood cultures and start empiric antibiotic therapy, adjusting based on pathogen identification and susceptibility results.
- Healthcare Professionals should administer these Cyanokit batches via an IV administration set equipped with a 0.2-micron inline filter with a polyethersulfone (PES) filtration membrane and having a membrane surface greater than or equal to 10 cm^2.

  Simultaneous administration of Cyanokit and blood products through the same IV line is not recommended.

Reporting Adverse Events

Healthcare Professionals should report any adverse reactions suspected of being due to Cyanokit to BTG International Inc at 1-877-377-3784 or email at infomed@serb.com and safety@serb.com.

Additionally, adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular Mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

This letter is not intended as a complete description of the benefits and risk related to the use of Cyanokit. Please refer to the enclosed full prescribing information.

Sincerely,

Signed by:
D9FB404FBCC441F...
Thomas Kolaras

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CYANOKIT safely and effectively. See full prescribing information for CYANOKIT.

CYANOKIT® (hydroxocobalamin for injection) for intravenous infusion
Initial U.S. Approval: 1975

----------INDICATIONS AND USAGE----------

CYANOKIT is indicated for the treatment of known or suspected cyanide poisoning. (1)

----------DOSAGE AND ADMINISTRATION----------

- If clinical suspicion of cyanide poisoning is high, administer CYANOKIT without delay and in conjunction with appropriate airway, ventilatory, and circulatory support, oxygen administration as well as management of seizures. (2.1)
- The expert advice of a regional poison control center may be obtained by calling 1-800-222-1222. (2.1)

Dosing:

- The starting dose of CYANOKIT for adults is 5 g, administered by intravenous infusion over 15 minutes. One 5 g vial is a complete starting dose. (2.2)
- Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by intravenous infusion for a total dose of 10 g. (2.2)
- The rate of infusion for the second 5 g dose may range from 15 minutes (for patients in extremis) to 2 hours based on patient condition. (2.2)
- The recommended diluent is 0.9% Sodium Chloride injection. (2.3)
- CYANOKIT requires a separate intravenous line for administration. (2.4)

----------DOSAGE FORMS AND STRENGTH----------

- CYANOKIT (hydroxocobalamin for injection) for intravenous infusion consists of 1 vial, containing 5 g lyophilized hydroxocobalamin dark red crystalline powder for injection. After reconstitution, the vial contains hydroxocobalamin for injection, 25 mg/mL. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Anaphylaxis and Other Hypersensitivity Reactions: Consider alternative therapies, if available, in patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. (5.2)
- Risk of Renal Injury: Acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals have been reported following CYANOKIT therapy. Monitor renal function for 7 days following CYANOKIT therapy. (5.3)
- Risk of Increased Blood Pressure: Substantial increases in blood pressure may occur following CYANOKIT therapy. Monitor blood pressure during treatment. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>5%) include transient chromaturia, erythema, oxalate crystals in urine, rash, increased blood pressure, nausea, headache, and infusion site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS contact BTG at 1-877-377-3784, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal studies, may cause fetal harm; however, CYANOKIT administration for cyanide poisoning may be lifesaving for the pregnant woman and fetus. Treatment should not be withheld due to pregnancy (8.1)
- Lactation: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION And FDA-approved patient labeling.

Revised: 05/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CYANOKIT is indicated for the treatment of known or suspected cyanide poisoning.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- If clinical suspicion of cyanide poisoning is high, administer CYANOKIT without delay.
- Comprehensive treatment of acute cyanide intoxication requires support of vital functions. Airway, ventilatory and circulatory support, oxygen administration, and management of seizures should not be delayed to administer CYANOKIT *[see Warnings and Precautions (5.1)]*.
- The expert advice of a regional poison control center may be obtained by calling 1-800-222-1222.

Identifying Patients with Cyanide Poisoning

Cyanide poisoning may result from inhalation, ingestion, or dermal exposure to various cyanide-containing compounds, including smoke from closed-space fires. Sources of cyanide poisoning include hydrogen cyanide and its salts, cyanogenic plants, aliphatic nitriles, and prolonged exposure to sodium nitroprusside.

The presence and extent of cyanide poisoning are often initially unknown. There is no widely available, rapid, confirmatory cyanide blood test. Treatment decisions must be made on the basis of clinical history and signs and symptoms of cyanide intoxication.

Table 1 Common Signs and Symptoms of Cyanide Poisoning

Symptoms	**Signs**
• Headache • Confusion • Dyspnea • Chest tightness • Nausea	• Altered Mental Status (e.g., confusion, disorientation) • Seizures or Coma • Mydriasis • Tachypnea / Hyperpnea (early) • Bradypnea / Apnea (late) • Hypertension (early) / Hypotension (late) • Cardiovascular collapse • Vomiting • Plasma lactate concentration ≥8 mmol/L

In some settings, panic symptoms including tachypnea and vomiting may mimic early cyanide poisoning signs. The presence of altered mental status (e.g., confusion and disorientation) and/or mydriasis is suggestive of true cyanide poisoning although these signs can occur with other toxic exposures as well.

Smoke Inhalation

Not all smoke inhalation victims will have cyanide poisoning and may present with burns, trauma, and exposure to other toxic substances making a diagnosis of cyanide poisoning particularly difficult. Prior to administration of CYANOKIT, smoke-inhalation victims should be assessed for the following:

- Exposure to fire or smoke in an enclosed area
- Presence of soot around the mouth, nose or oropharynx
- Altered mental status

Although hypotension is highly suggestive of cyanide poisoning, it is only present in a small percentage of cyanide-poisoned smoke inhalation victims. Also indicative of cyanide poisoning is a plasma lactate concentration ≥10 mmol/L (a value higher than that typically listed in the table of signs and symptoms of isolated cyanide poisoning because carbon monoxide associated with smoke inhalation also contributes to lactic acidemia). If cyanide poisoning is suspected, treatment should not be delayed to obtain a plasma lactate concentration.

Use with Other Cyanide Antidotes

The safety of administering other cyanide antidotes simultaneously with CYANOKIT has not been established. If a decision is made to administer another cyanide antidote with CYANOKIT, these drugs should not be administered concurrently in the same intravenous line *[see Dosage and Administration (2.4)]*.

2.2 Recommended Dosing

The starting dose of hydroxocobalamin for adults is 5 g administered as an intravenous infusion over 15 minutes (approximately 15 mL/min). Administration of the entire vial constitutes a complete starting dose. Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by intravenous infusion for a total dose of 10 g. The rate of infusion for the second dose may range from 15 minutes (for patients in extremis) to two hours, as clinically indicated.

2.3 Preparation of Solution for Infusion

Reconstitute the 5 g vial of hydroxocobalamin with 200 mL of diluent (not provided with CYANOKIT) using the supplied sterile transfer spike. The recommended diluent is 0.9% Sodium Chloride injection (0.9% NaCl). Lactated Ringers injection and 5% Dextrose injection (D5W) have also been found to be compatible with hydroxocobalamin and may be used if 0.9% NaCl is not readily available. The line on the vial label represents 200 mL volume of diluent. Following the addition of diluent to the lyophilized powder, the vial should be repeatedly inverted or rocked, not shaken, for at least 60 seconds prior to infusion.

Visually inspect hydroxocobalamin solutions for particulate matter and color prior to administration. If the reconstituted solution is not dark red or if particulate matter is observed after the solution has been appropriately mixed, the solution should be discarded.

2.4 Incompatibility Information

Physical incompatibility (particle formation) and chemical incompatibility were observed with the mixture of hydroxocobalamin in solution with selected drugs that are frequently used in resuscitation efforts. Hydroxocobalamin is also chemically incompatible with sodium thiosulfate and sodium nitrite and has been reported to be incompatible with ascorbic acid. Therefore, these and other drugs should not be administered simultaneously through the same intravenous line as hydroxocobalamin.

Simultaneous administration of hydroxocobalamin and blood products (whole blood, packed red cells, platelet concentrate and/or fresh frozen plasma) through the same intravenous line is not recommended. However, blood products and hydroxocobalamin can be administered simultaneously using separate intravenous lines (preferably on contralateral extremities, if peripheral lines are being used).

2.5 Storage of Reconstituted Drug Product

Once reconstituted, hydroxocobalamin is stable for up to 6 hours at temperatures not exceeding 40°C (104°F). Do not freeze. Any reconstituted product not used by 6 hours should be discarded.

3 DOSAGE FORMS AND STRENGTHS

CYANOKIT (hydroxocobalamin for injection) for intravenous infusion consists of 1 vial, containing 5 g lyophilized hydroxocobalamin dark red crystalline powder for injection. After reconstitution, the vial contains hydroxocobalamin for injection, 25 mg/mL *[see How Supplied/Storage and Handling (16) for full kit description]*.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Emergency Patient Management

In conjunction with CYANOKIT, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of seizures. Consideration should be given to decontamination measures based on the route of exposure.

5.2 Risk of Anaphylactic and Other Hypersensitivity Reactions

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consider alternative therapies, if available.

Allergic reactions may include: anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, and rash.

Allergic reactions including angioneurotic edema have also been reported in postmarketing experience.

5.3 Risk of Renal Injury

Cases of acute renal failure with acute tubular necrosis, renal impairment, and urine calcium oxalate crystals have been reported. In some situations, hemodialysis was required to achieve recovery. Regular monitoring of renal function, including but not limited to blood urea nitrogen (BUN) and serum creatinine, should be performed for 7 days following CYANOKIT therapy.

5.4 Risk of Increased Blood Pressure

Many patients with cyanide poisoning will be hypotensive; however, elevations in blood pressure have also been observed in known or suspected cyanide poisoning victims.

Elevations in blood pressure (≥180 mmHg systolic or ≥110 mmHg diastolic) were observed in approximately 18% of healthy subjects (not exposed to cyanide) receiving hydroxocobalamin 5 g and 28% of subjects receiving 10 g. Increases in blood pressure were noted shortly after the infusions were started; the maximal increase in blood pressure was observed toward the end of the infusion. These elevations were generally transient and returned to baseline levels within 4 hours of dosing. Monitor blood pressure during treatment with CYANOKIT.

5.5 Interference with Clinical Laboratory Evaluations and Clinical Methods

Clinical Laboratory Evaluations

Because of its deep red color, hydroxocobalamin has been found to interfere with colorimetric determination of certain laboratory parameters (e.g., clinical chemistry, hematology, coagulation, and urine parameters). *In vitro*

tests indicated that the extent and duration of the interference are dependent on numerous factors such as the dose of hydroxocobalamin, analyte, methodology, analyzer, hydroxocobalamin concentration, and partially on the time between sampling and measurement.

The data presented in Table 2 is collected from *in vitro* studies and pharmacokinetic data in healthy volunteers and describes laboratory interference that may be observed following a 5 g dose of hydroxocobalamin. Interference following a 10 g dose can be expected to last up to an additional 24 hours. The extent and duration of interference in cyanide-poisoned patients may differ. In addition, results may vary substantially from one analyzer to another. Be aware of this when reporting and interpreting laboratory results.

Table 2 Laboratory Interference Observed with *in vitro* Samples of Hydroxocobalamin

Laboratory Parameter	No Interference Observed	Artificially Increased *	Artificially Decreased *	Un-predictable	Duration of Interference
Clinical Chemistry	Calcium Sodium Potassium Chloride Urea GGT	Creatinine Bilirubin Triglycerides Cholesterol Total protein Glucose Albumin Alkaline phosphatase	ALT Amylase	Phosphate Uric Acid AST CK CKMB LDH	24 hours with the exception of bilirubin (up to 4 days)
Hematology	Erythrocytes Hematocrit MCV Leukocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets	Hemoglobin MCH MCHC Basophils			12 - 16 hours
Coagulation				aPTT PT (Quick or INR)	24 - 48 hours
Urinalysis		pH (with all doses) Glucose Protein Erythrocytes Leukocytes Ketones Bilirubin Urobilinogen Nitrite	pH (with equivalent doses of <5 g)		48 hours up to 8 days; color changes may persist up to 28 days

* ≥10% interference observed on at least 1 analyzer
Analyzers used: ACL Futura (Instrumentation Laboratory), AxSYM®/Architect™ (Abbott), BM Coasys[110] (Boehringer Mannheim), CellDyn 3700® (Abbott), Clinitek® 500 (Bayer), Cobas Integra® 700, 400 (Roche), Gen-S Coultronics, Hitachi 917, STA® Compact, Vitros® 950 (Ortho Diagnostics)

Clinical Methods

Because of its deep red color, hydroxocobalamin may cause hemodialysis machines to shut down due to an erroneous detection of a "blood leak". This should be considered before hemodialysis is initiated in patients treated with hydroxocobalamin.

5.6 Photosensitivity

Hydroxocobalamin absorbs visible light in the UV spectrum. It therefore has potential to cause photosensitivity. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discolored.

5.7 Use of Blood Cyanide Assay

While determination of blood cyanide concentration is not required for management of cyanide poisoning and should not delay treatment with CYANOKIT, collecting a pretreatment blood sample may be useful for documenting cyanide poisoning as sampling post-CYANOKIT use may be inaccurate.

6 ADVERSE REACTIONS

Serious adverse reactions with hydroxocobalamin include allergic reactions, renal injury, and increases in blood pressure *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

6.1 Clinical Studies Experience

Experience in Healthy Subjects

Because clinical trials were conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice.

A double-blind, randomized, placebo-controlled, single-ascending-dose (2.5, 5, 7.5, and 10 g) study was conducted to assess the safety, tolerability, and pharmacokinetics of hydroxocobalamin in 136 healthy adult subjects. Because of the dark red color of hydroxocobalamin, the two most frequently occurring adverse reactions were chromaturia (red-colored urine) which was reported in all subjects receiving a 5 g dose or greater; and erythema (skin redness), which occurred in most subjects receiving a 5 g dose or greater. Adverse reactions reported in at least 5% of the 5 g dose group and corresponding rates in the 10 g and placebo groups are shown in Table 3.

Table 3 Incidence of Adverse Reactions Occurring in >5% of Subjects in 5 g Dose Group and Corresponding Incidence in 10 g Dose Group and Placebo

	5 g Dose Group		10 g Dose Group	
ADR	**Hydroxocobalamin N=66 n (%)**	**Placebo N=22 n (%)**	**Hydroxocobalamin N=18 n (%)**	**Placebo N=6 n (%)**
Chromaturia (red colored urine)	66 (100)	0	18 (100)	0
Erythema	62 (94)	0	18 (100)	0
Oxalate crystals in urine	40 (61)	1 (5)	10 (56)	0
Rash*	13 (20)	0	8 (44)	0
Blood pressure increased	12 (18)	0	5 (28)	0
Nausea	4 (6)	1 (5)	2 (11)	0
Headache	4 (6)	1 (5)	6 (33)	0
Lymphocyte percent decreased	5 (8)	0	3 (17)	0
Infusion site reaction	4 (6)	0	7 (39)	0

* Rashes were predominantly acneiform

In this study, the following adverse reactions were reported to have occurred in a dose-dependent fashion and with greater frequency than observed in placebo-treated cohorts: increased blood pressure (particularly diastolic blood pressure), rash, nausea, headache and infusion site reactions. All were mild to moderate in severity and resolved spontaneously when the infusion was terminated or with standard supportive therapies.

Other adverse reactions reported in this study and considered clinically relevant were:

- *Eye disorders:* swelling, irritation, redness

- *Gastrointestinal disorders:* dysphagia, abdominal discomfort, vomiting, diarrhea, dyspepsia, hematochezia
- *General disorders and administration site conditions:* peripheral edema, chest discomfort
- *Immune system disorders:* allergic reaction
- *Nervous system disorders:* memory impairment, dizziness
- *Psychiatric disorders:* restlessness
- *Respiratory, thoracic and mediastinal disorders:* dyspnea, throat tightness, dry throat
- *Skin and subcutaneous tissue disorders:* urticaria, pruritus
- *Vascular disorders:* hot flush

Experience in Known or Suspected Cyanide Poisoning Victims

Four open-label, uncontrolled, clinical studies (one of which was prospective and three of which were retrospective) were conducted in known or suspected cyanide-poisoning victims. A total of 245 patients received hydroxocobalamin treatment in these studies. Systematic collection of adverse events was not done in all of these studies and interpretation of causality is limited due to the lack of a control group and due to circumstances of administration (e.g., use in fire victims). Adverse reactions reported in these studies listed by system organ class included:

- *Cardiac disorders:* ventricular extrasystoles
- *Investigations:* electrocardiogram repolarization abnormality, heart rate increased
- *Respiratory, thoracic, and mediastinal disorders:* pleural effusion

Adverse reactions common to both the studies in known or suspected cyanide poisoning victims and the study in healthy volunteers are listed in the healthy volunteer section only and are not duplicated in this list.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CYANOKIT. Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Cases of acute renal failure with acute tubular necrosis, renal impairment, and urine calcium oxalate crystals have been reported in patients treated with CYANOKIT.

7 DRUG INTERACTIONS

Formal drug interaction studies have not been conducted with CYANOKIT.

Interference with Laboratory Tests

Because of its deep red color, hydroxocobalamin has been found to interfere with colorimetric determination of certain laboratory parameters (e.g., clinical chemistry, hematology, coagulation, and urine parameters). Be aware of this when reporting and interpreting laboratory results *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from cases reported in the published literature and postmarketing surveillance with CYANOKIT use in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage, or adverse maternal and fetal outcomes. There are risks to the pregnant woman and fetus associated with untreated

cyanide poisoning *(see Clinical Considerations)*. In animal studies, hydroxocobalamin administered to pregnant rats and rabbits during the period of organogenesis caused skeletal and soft tissue abnormalities, including alterations in the central nervous system, at exposures similar to human exposures at the therapeutic dose *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Cyanide readily crosses the placenta. Cyanide poisoning is a medical emergency in pregnancy which can be fatal for the pregnant woman and fetus if left untreated. Life-sustaining therapy should not be withheld due to pregnancy.

Data

Animal Data

In animal studies, pregnant rats and rabbits received CYANOKIT (75, 150, or 300 mg/kg/d) during the period of organogenesis. Following intraperitoneal dosing in rats and intravenous dosing in rabbits, maternal exposures were equivalent to 0.5, 1, or 2 times the human exposure at the therapeutic dose (based on AUC). In the high dose groups for both species, maternal toxicity occurred, and there was a reduced number of live fetuses due to embryofetal resorptions. In addition, decreased live fetal weight occurred in high dose rats, but not in rabbits. Incomplete skeletal ossification occurred in both rats and rabbits. In rats, two fetuses of the high dose group and two fetuses of the mid dose group (each from a different litter) had short, rudimentary or small front or hind legs. Rabbit litters and fetuses exhibited a dose-dependent increase in various gross soft tissue and skeletal anomalies. The main findings in rabbits were flexed, rigid flexor or medially rotated forelimbs or hindlimbs and domed heads at external examination; enlarged anterior or posterior fontanelles of the ventricles of the brain and flat, bowed or large ribs at skeletal examination; and dilated ventricles of the brain, and thick wall of the stomach at visceral examination. It is unknown if similar findings would be observed in rats and rabbits if CYANOKIT was administered as a single dose during any critical period of development.

8.2 Lactation

Risk Summary

Breastfeeding is not recommended during treatment with CYANOKIT. There are no data to determine when breastfeeding may be safely restarted following administration of CYANOKIT. Hydroxocobalamin and Vitamin B12 (which is formed when hydroxocobalamin combines with cyanide) are present in human milk. There are no data on the effects of hydroxocobalamin on the breastfed infant or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness of CYANOKIT have not been established in this population. In non-US marketing experience, a dose of 70 mg/kg has been used to treat pediatric patients.

8.5 Geriatric Use

Approximately 50 known or suspected cyanide poisoning victims aged 65 or older received hydroxocobalamin in clinical studies. In general, the safety and effectiveness of hydroxocobalamin in these patients was similar to that of younger patients. No adjustment of dose is required in elderly patients.

8.6 Renal Impairment

The safety and effectiveness of CYANOKIT have not been studied in patients with renal impairment. Hydroxocobalamin and cyanocobalamin are eliminated unchanged by the kidneys.

8.7 Hepatic Impairment

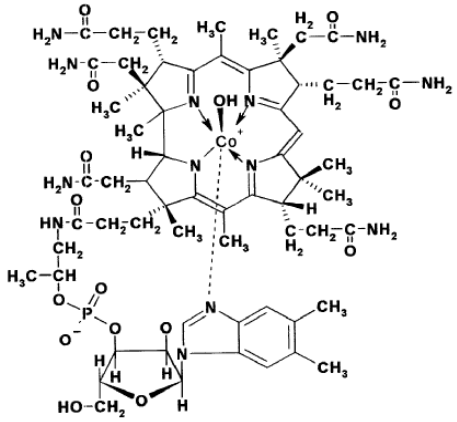
The safety and effectiveness of CYANOKIT have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No data are available about overdose with CYANOKIT in adults. Should overdose occur, treatment should be directed to the management of symptoms. Hemodialysis may be effective in such a circumstance, but is only indicated in the event of significant hydroxocobalamin-related toxicity. Because of its deep red color, hydroxocobalamin may interfere with the performance of hemodialysis machines *[see Warnings and Precautions (5.5)]*.

11 DESCRIPTION

Hydroxocobalamin, the active ingredient in CYANOKIT, is cobinamide dihydroxide dihydrogen phosphate (ester), mono (inner salt), 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-1H-benzimidazole, an antidote. The drug substance is the hydroxylated active form of vitamin B_{12} and is a large molecule in which a trivalent cobalt ion is coordinated in four positions by a tetrapyrol (or corrin) ring. It is a hygroscopic, odorless, dark red, crystalline powder that is freely soluble in water and ethanol, and practically insoluble in acetone and diethyl ether. Hydroxocobalamin has a molecular weight of 1346.36 atomic mass units, an empirical formula of $C_{62}H_{89}CoN_{13}O_{15}P$ and the following structural formula:



CYANOKIT (hydroxocobalamin for injection) for intravenous infusion is a cyanide antidote package which contains one colorless 250 mL glass vial, containing 5 g dark red lyophilized hydroxocobalamin, pH adjusted with hydrochloric acid, one transfer spike, one intravenous administration set, one quick use reference guide and one package insert.

The 5 g vial of hydroxocobalamin for injection is to be reconstituted with 200 mL of 0.9% NaCl, to give a dark red injectable solution (25 mg/mL). If 0.9% NaCl is not readily available, 200 mL of either Lactated Ringers injection or 5% Dextrose injection (D5W) may be used as the diluent. Diluent is not included in the CYANOKIT. The pH of the reconstituted product ranges from 3.5 to 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyanide is an extremely toxic poison. In the absence of rapid and adequate treatment, exposure to a high dose of cyanide can result in death within minutes due to the inhibition of cytochrome oxidase resulting in arrest of cellular respiration. Specifically, cyanide binds rapidly with cytochrome a3, a component of the cytochrome c oxidase complex in mitochondria. Inhibition of cytochrome a3 prevents the cell from using oxygen and forces anaerobic metabolism, resulting in lactate production, cellular hypoxia and metabolic acidosis. In massive acute cyanide poisoning, the mechanism of toxicity may involve other enzyme systems as well. Signs and symptoms of acute systemic cyanide poisoning may develop rapidly within minutes, depending on the route and extent of cyanide exposure.

The action of CYANOKIT in the treatment of cyanide poisoning is based on its ability to bind cyanide ions. Each hydroxocobalamin molecule can bind one cyanide ion by substituting it for the hydroxo ligand linked to the trivalent cobalt ion, to form cyanocobalamin, which is then excreted in the urine.

12.2 Pharmacodynamics

Administration of CYANOKIT to cyanide-poisoned patients with the attendant formation of cyanocobalamin resulted in increases in blood pressure and variable changes in heart rate upon initiation of hydroxocobalamin infusions *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

Following intravenous administration of hydroxocobalamin significant binding to plasma proteins and low molecular weight physiological compounds occurs, forming various cobalamin-(III) complexes by replacing the hydroxo ligand. The low molecular weight cobalamins-(III) formed, including hydroxocobalamin, are termed "free cobalamins-(III)"; the sum of free and protein-bound cobalamins is termed "total cobalamins-(III)". In order to reflect the exposure to the sum of all derivatives, pharmacokinetics of cobalamins-(III) (i.e., cobalamin-(III) entity without specific ligand) were investigated instead of hydroxocobalamin alone, using the concentration unit µg eq/mL.

Dose-proportional pharmacokinetics was observed following single dose intravenous administration of 2.5 to 10 g of hydroxocobalamin in healthy volunteers. Mean free and total cobalamins-(III) C_{max} values of 113 and 579 µg eq/mL, respectively, were determined following a dose of 5 g of hydroxocobalamin. Similarly, mean free and total cobalamins-(III) C_{max} values of 197 and 995 µg eq/mL, respectively, were determined following the dose of 10 g of hydroxocobalamin.

When normalized for body weight, male and female subjects revealed no major differences in pharmacokinetic parameters of free and total cobalamins-(III) following the administration of 5 and 10 g of hydroxocobalamin.

Distribution

The volume of distribution at steady state (V_{ss}) for both free and total cobalamins-(III) showed no apparent relationship to dose. The V_{ss} ranged from 280.7 to 349.5 L for free cobalamins-(III), and from 21.8 to 25.6 L for total cobalamins-(III). The comparatively high values for V_{ss} of free cobalamins-(III) are due to the high protein binding of hydroxocobalamin as it reacts in the blood with plasma constituents to form cobalamins-(III) complexes and the rapid distribution of free cobalamins-(III) into tissues.

Elimination

The mean total amount of cobalamins-(III) excreted in urine during the collection period of 72 hours was about 60% of a 5 g dose and about 50% of a 10 g dose of hydroxocobalamin. Overall, the total urinary excretion was

calculated to be at least 60 to 70% of the administered dose. The majority of the urinary excretion occurred during the first 24 hours, but red-colored urine was observed for up to 35 days following the intravenous infusion. The mean half-life of free and total cobalamins-(III) was found to be approximately 26 to 31 hours at both the 5 g and 10 g dose level.

Metabolism
Hydroxocobalamin does not undergo metabolism.

Excretion
Hydroxocobalamin is mainly excreted in urine.

In cyanide poisoning victims, hydroxocobalamin binds to cyanide to form cyanocobalamin, which is mainly excreted in urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term animal studies have not been performed to evaluate the carcinogenic potential of hydroxocobalamin.

Mutagenesis
Hydroxocobalamin was negative in the following mutagenicity assays: *in vitro* bacterial reverse mutation assay using *Salmonella typhimurium* and *Escherichia coli* strains, an *in vitro* assay of the tk locus in mouse lymphoma cells, and an *in vivo* rat micronucleus assay.

Impairment of Fertility
The effect of hydroxocobalamin on fertility has not been evaluated.

14 CLINICAL STUDIES

14.1 Animal Efficacy (Dog) Study of CYANOKIT for Cyanide Poisoning

The effectiveness of CYANOKIT for treatment of cyanide poisoning has not been determined in humans because inducing cyanide poisoning in humans to study the drug's efficacy is not ethical. Therefore, the effectiveness of CYANOKIT for cyanide poisoning was established based on the results of the adequate and well-controlled animal efficacy study described below. While the results of this animal study cannot be extrapolated to humans with certainty, the extrapolation is supported by the understanding of the pathophysiologic mechanisms of the toxicity of cyanide and the mechanisms of the protective effect of hydroxocobalamin as examined in dogs. In addition, the results of uncontrolled human studies and the animal study establish that hydroxocobalamin is likely to produce clinical benefit in humans.

The effectiveness of hydroxocobalamin was examined in a randomized, placebo-controlled, blinded study in cyanide-poisoned adult dogs assigned to treatment with vehicle (0.9% saline), or 75 or 150 mg/kg hydroxocobalamin. Anesthetized dogs were poisoned by intravenous administration of a lethal dose of potassium cyanide. Dogs then received vehicle or 75 or 150 mg/kg hydroxocobalamin, administered intravenously over 7.5 minutes. The 75 and 150 mg/kg doses are approximately equivalent to 5 and 10 g of hydroxocobalamin (respectively) in humans based on both body weight and the C_{max} of hydroxocobalamin (total cobalamins-(III)). Survival at 4 hours and at 14 days was significantly greater in low-and high-dose groups compared with dogs receiving vehicle alone (Table 4). Hydroxocobalamin reduced whole blood cyanide concentrations by approximately 50% by the end of the infusion compared with vehicle.

Table 4 Survival of Cyanide-Poisoned Dogs

Parameter	Treatment		
		CYANOKIT	
	Vehicle N=17	75 mg/kg N=19	150 mg/kg N=18
Survival at Hour 4, n (%)	7 (41)	18 (95)	18 (100)
Survival at Day 14, n (%)	3 (18)	15 (79)	18 (100)

Histopathology revealed brain lesions that were consistent with cyanide-induced hypoxia. The incidence of brain lesions was markedly lower in hydroxocobalamin treated animals compared to vehicle treated groups.

14.2 Smoke Inhalation Victims

A prospective, uncontrolled, open-label study was carried out in 69 subjects who had been exposed to smoke inhalation from fires. Subjects had to be over 15 years of age, present with soot in the mouth and expectoration (to indicate significant smoke exposure), and have altered neurological status. The median hydroxocobalamin dose was 5 g with a range from 4 to 15 g.

Fifty of 69 subjects (73%) survived following treatment with hydroxocobalamin. Nineteen subjects treated with hydroxocobalamin did not survive. Fifteen patients treated with hydroxocobalamin were in cardiac arrest initially at the scene; 13 of these subjects died and 2 survived.

Of the 42 subjects with pretreatment cyanide levels considered to be potentially toxic, 28 (67%) survived. Of the 19 subjects whose pretreatment cyanide levels were considered potentially lethal, 11 (58%) survived. Of the 50 subjects who survived, 9 subjects (18%) had neurological sequelae at hospital discharge. These included dementia, confusion, psychomotor retardation, anterograde amnesia, intellectual deterioration moderate cerebellar syndrome, aphasia, and memory impairment.

Two additional retrospective, uncontrolled studies were carried out in subjects who had been exposed to cyanide from fire or smoke inhalation. Subjects were treated with up to 15 g of hydroxocobalamin. Survival in these two studies was 34 of 61 (56%) for one study, and 30 of 72 (42%) for the second.

14.3 Cyanide Poisoning by Ingestion or Inhalation

A retrospective, uncontrolled study was carried out in 14 subjects who had been exposed to cyanide from sources other than from fire or smoke (i.e., ingestion or inhalation). Subjects were treated with 5 to 20 g of hydroxocobalamin. Eleven of 12 subjects whose blood cyanide concentration was known had initial blood cyanide levels considered to be above the lethal threshold.

Ten of 14 subjects (71%) survived, following administration of hydroxocobalamin. One of the four subjects who died had presented in cardiac arrest. Of the 10 subjects who survived, only 1 subject had neurological sequelae at hospital discharge. This subject had post-anoxic encephalopathy, with memory impairment, considered to be due to cyanide poisoning.

14.4 Cross-Study Findings

<u>Experience with Dosing Greater than 10 g of Hydroxocobalamin</u>
Across all four uncontrolled studies, 10 patients who did not demonstrate a full response to 5 or 10 g-doses of hydroxocobalamin were treated with more than 10 g of hydroxocobalamin. One of these 10 patients survived with unspecified neurological sequelae.

Effects on Blood Pressure
Initiation of hydroxocobalamin infusion as part of the therapeutic interventions generally resulted in increases in blood pressure and variable changes in heart rate (often normalization).

Survival of Patients Presenting in Cardiac Arrest
Of the 245 patients across all four studies, 68 (28%) presented in cardiac arrest. While blood pressure and heart rate may have been restored in many of these 68 patients, only five (7%) survived.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each CYANOKIT carton (NDC 50633-310-11) consists of the following:

- One 250 mL glass vial, containing lyophilized hydroxocobalamin for injection, 5 g
- One sterile transfer spike
- One sterile intravenous infusion set
- One quick use reference guide
- One package insert

Diluent is not included.

Storage
Lyophilized form
Store at 25°C (77°F); excursions permitted to 15-30°C (59 to 86°F) [see USP Controlled Room Temperature].

CYANOKIT may be exposed during short periods to the temperature variations of usual transport (15 days submitted to temperatures ranging from 5 to 40°C (41 to 104°F), transport in the desert (4 days submitted to temperatures ranging from 5 to 60°C (41 to 140°F)) and freezing/defrosting cycles (15 days submitted to temperatures ranging from -20 to 40°C (-4 to 104°F)).

Reconstituted solution
Store up to 6 hours at a temperature not exceeding 40ºC (104°F). Do not freeze. Discard any unused portion after 6 hours.

17 PATIENT COUNSELING INFORMATION

CYANOKIT is indicated for cyanide poisoning and in this setting, patients will likely be unresponsive or may have difficulty in comprehending counseling information.

Erythema and Chromaturia
Advise patients that skin redness may last up to 2 weeks and urine coloration may last for up to 5 weeks after administration of CYANOKIT. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discolored.

Rash

Inform patients that an acneiform rash may appear anywhere from 7 to 28 days following hydroxocobalamin treatment. This rash will usually resolve without treatment within a few weeks.

Renal Function Monitoring
Advise patients that renal function will be monitored for 7 days following treatment with CYANOKIT or, in the event of renal impairment, until renal function returns to normal.

Pregnancy

Advise pregnant women that maternal cyanide poisoning results in fetal cyanide poisoning. Treatment for cyanide poisoning may be lifesaving for both the pregnant woman and fetus. Advise females of reproductive potential to notify their provider if they were pregnant during therapy with CYANOKIT *[see USE IN SPECIFIC POPULATIONS (8.1)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with CYANOKIT *[see USE IN SPECIFIC POPULATIONS (8.2)]*.

Patient Information
CYANOKIT (hydroxocobalamin for injection)
for intravenous infusion

What is CYANOKIT?

CYANOKIT is prescription medicine used for the treatment of known or suspected cyanide poisoning. Cyanide is a chemical poison. Cyanide poisoning can happen from:
breathing smoke from household and industrial fires
breathing or swallowing cyanide
having your skin exposed to cyanide

The effectiveness of CYANOKIT was based on a study in animals, because intentionally exposing humans to cyanide is not ethical. The safety of CYANOKIT was studied in animals and healthy people and derived from experience in patients exposed to cyanide.

It is not known if CYANOKIT is safe and effective in children.

Cyanide poisoning is a life-threatening condition because cyanide stops your body from being able to use oxygen. You can die if your body does not have enough oxygen.

Tell your healthcare provider if you:

- have had an allergic reaction to hydroxocobalamin or cyanocobalamin
- **are pregnant or think you may have been pregnant during treatment with CYANOKIT**. CYANOKIT may harm your unborn baby. However, treatment for cyanide poisoning may save your life and the life of your unborn baby.
- **are breastfeeding.** Breastfeeding is not recommended during treatment with CYANOKIT. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How is CYANOKIT given?

- Your healthcare provider will give you CYANOKIT through a vein by intravenous (IV) infusion over 15 minutes.
- A second dose of CYANOKIT may be given to you if needed.

What should I avoid after I receive CYANOKIT?

- CYANOKIT may cause red colored skin. Skin redness is common during treatment with CYANOKIT and may last up to 2 weeks after treatment with CYANOKIT. You should avoid sunlight while your skin is red.

What are the possible side effects of CYANOKIT?

CYANOKIT may cause serious side effects, including:

- **Allergic reactions**. Signs and symptoms of a serious allergic reaction include chest tightness, trouble breathing, swelling, hives, itching, and rash. Seek emergency help if you experience signs and/or symptoms of an allergic reaction.
- **Kidney problems**. CYANOKIT can cause kidney problems, including kidney failure. Tell your healthcare provider if you develop crystals in your urine. Your healthcare provider will monitor your kidney function for 7 days after treatment with CYANOKIT, or longer if needed.
- **Increased blood pressure.** Increased blood pressure is a common but serious side effect during treatment with CYANOKIT. Your healthcare provider will monitor your blood pressure during treatment with CYANOKIT.

The most common side effects of CYANOKIT include:

- red colored urine. Red colored urine redness may last up to 5 weeks after treatment with CYANOKIT.
- acne-like rash. Acne-like rash may appear 7 to 28 days after treatment with CYANOKIT. This rash usually goes away without any treatment.
- nausea
- headache
- reactions at the site of infusion

These are not all the side effects with CYANOKIT.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of CYANOKIT.

This Patient Information leaflet summarizes the most important information about CYANOKIT. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about CYANOKIT that is written for health professionals.

What are the ingredients in CYANOKIT?

Active ingredient: hydroxocobalamin

Manufactured by: Merck Santé s.a.s., Semoy, France
Distributed by BTG International Inc. West Conshohocken, PA 19428

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 05/2021