The Danger of Cyanide May Remain

Full Starting Dose in a Single Vial

SELECTED SAFETY INFORMATION

Cyanide poisoning may result from inhalation, ingestion, or dermal exposure. Prior to administration of CYANOKIT, smoke-inhalation victims should be assessed for: exposure to fire or smoke in an enclosed area, presence of soot around the mouth, nose, or oropharynx, and altered mental status. In addition to CYANOKIT, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity.

Please see Important Safety Information on page 6 and accompanying full Prescribing Information.
**Suspect Cyanide**

**Cyanide (CN) is an often unrecognized danger in closed-space fires**

- CN can be released by **virtually any material containing carbon and nitrogen** when burned under high temperature and low oxygen conditions\(^1\,^2\)

- There is potential for CN toxicity due to the increased use of **synthetic materials that produce CN during combustion in closed-space fires**\(^2\)

**Cyanide—A deadly toxin**

- Moderate to high concentrations of CN can cause **severe injury or death within minutes**\(^3\)

- CN poisoning may also cause **central nervous system side effects** including intellectual impairment, Parkinson-type effects, and personality changes\(^4\)

**Common building materials known to release high levels of CN during combustion\(^5\)**

<table>
<thead>
<tr>
<th>Material</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass fiber</td>
<td>(building insulation wool)</td>
</tr>
<tr>
<td>Melamine</td>
<td>(laminate for building construction)</td>
</tr>
<tr>
<td>PIR</td>
<td>(thermal insulation foam)</td>
</tr>
<tr>
<td>Nitrile rubber</td>
<td>(tubing insulation)</td>
</tr>
<tr>
<td>Rigid PUR</td>
<td>(building insulation foam)</td>
</tr>
<tr>
<td>Particle board</td>
<td>(laminate for building base material)</td>
</tr>
</tbody>
</table>

*Items pictured may not be accurate representations.
Difficult to Diagnose

Diagnostic Challenges in the Treatment of Smoke-Inhalation Victims

- Currently, there is no diagnostic test to confirm CN poisoning within the limited window for initiating potentially lifesaving intervention\(^6,7\).
  - Even at most hospitals, rapid measurements of CN are not available\(^6,7\).
  - Lactate levels may be tested as levels increase proportionally with the amount of CN poisoning because of the metabolic acidosis\(^8,9\).
- CN and carbon monoxide (CO) poisoning can be difficult to differentiate due to common signs and symptoms\(^6\).

Moderate to Severe Poisoning Signs/Symptoms\(^6,8\)

<table>
<thead>
<tr>
<th>CN</th>
<th>COMMON TO BOTH</th>
<th>CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular collapse</td>
<td>Altered level of consciousness</td>
<td>Severe headache</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Respiratory arrest</td>
<td>Shock and death</td>
</tr>
<tr>
<td>Almond odor on breath</td>
<td>Cardiac dysrhythmia</td>
<td></td>
</tr>
<tr>
<td>(may not be detectable)</td>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidemia</td>
<td></td>
</tr>
</tbody>
</table>

- Because CN poisoning prevents cells from using oxygen (O\(_2\)), signs and symptoms of CN poisoning also mimic those of O\(_2\) deprivation\(^10\).
When to Suspect Cyanide Poisoning

There is no rapid test to confirm CN poisoning—
The decision to treat empirically could save lives³

CN poisoning in smoke-inhalation victims should be suspected if the following manifestations are present³,⁵¹:

- Exposure to fire or smoke in an enclosed area
- Soot around mouth, nose, or back of mouth
- Altered mental status (e.g., confusion, disorientation)

*List may not be comprehensive.

References:
10. Schnopp R. Where there’s fire—there’s smoke! In: Smoke: Cyanide and Carbon Monoxide: The Toxic Twins of Smoke Inhalation. Indianapolis, IN: Cyanide Poisoning Treatment Coalition; 2009:3-5.
CLINICAL STUDY EXPERIENCE

- A controlled animal study demonstrated efficacy in cyanide-poisoned adult dogs; due to ethical considerations, no controlled human efficacy studies have been performed\(^ \text{11,12} \)

- In an uncontrolled, open-label, prospective study, empiric administration of hydroxocobalamin was associated with survival among 67% of patients (N=69) confirmed a posteriori to have had cyanide poisoning\(^ \text{11,13} \)

—The most common hydroxocobalamin-related adverse events were chromaturia, red skin discoloration, hypertension, erythema, and increased blood pressure\(^ \text{11,13} \)

- It has been shown that the concentration of blood lactate increases proportionally with the severity of CN poisoning, and that hydroxocobalamin treatment results in rapid resolution of CN-induced lactic acidemia\(^ \text{8,9,14} \)

EXPERIENCE

- CYANOKIT has been used to treat multiple sources of CN poisoning including smoke inhalation and ingestion\(^ \text{11,13,15,16} \)

- Hydroxocobalamin has been used in France since 1996 and in the U.S. since 2007 to treat known or suspected CN poisoning\(^ \text{16} \)

SAFETY CONDUCIVE TO EMPIRIC USE\(^ \text{17,18} \)

- Studies have shown CYANOKIT to be well-tolerated even in the absence of cyanide poisoning\(^ \text{11,13,15,17} \)

DESIGNED FOR USE ON THE SCENE OR IN THE HOSPITAL

- Full starting dose in a single vial
- Prepare and administer in 3 steps
- Portable packaging

SELECTED SAFETY INFORMATION

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of 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.

Please see Important Safety Information on page 6 and accompanying full Prescribing Information.
INDICATION

CYANOKIT (hydroxocobalamin for injection) 5 g for intravenous infusion is indicated for the treatment of known or suspected cyanide poisoning. If clinical suspicion of cyanide poisoning is high, CYANOKIT should be administered without delay.

IMPORTANT SAFETY INFORMATION

Cyanide poisoning may result from inhalation, ingestion, or dermal exposure. Prior to administration of CYANOKIT, smoke-inhalation victims should be assessed for: exposure to fire or smoke in an enclosed area; presence of soot around the mouth, nose, or oropharynx; and altered mental status. In addition to CYANOKIT, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity.

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of 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.

Substantial increases in blood pressure may occur following CYANOKIT therapy. Elevations in blood pressure (≥180 mmHg systolic or ≥110 mmHg diastolic) were observed in approximately 18% of healthy subjects receiving hydroxocobalamin 5 g and 28% of subjects receiving 10 g.

Usage may interfere with some clinical laboratory evaluations. Also, 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. Due to potential photosensitivity, patients should avoid direct sun until erythema resolves.

CYANOKIT is Pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk. Safety and effectiveness of CYANOKIT have not been established in pediatric patients.

The most common adverse reactions (>5%) included transient chromaturia, erythema, rash (predominantly acneiform), increased blood pressure, nausea, headache, decreased lymphocyte percentage, and injection site reactions.

Please see accompanying full Prescribing Information.

For additional resources, grant information, and product information, visit CYANOKIT.com.

CYANOKIT is a registered trademark of Merck Santé s.a.s., licensed by Meridian Medical Technologies, Inc., a Pfizer company.
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) 5 g for intravenous infusion
Initial U.S. Approval: 1975

Recommended Dosing (2.1) 4/2011
Preparation of Solution for Infusion (2.2) 4/2011
Interference with Clinical Laboratory Evaluations and Clinical Methods (5.5) 4/2011

INDICATIONS AND USAGE
Cyanokit contains hydroxocobalamin, an antidote indicated for the treatment of known or suspected cyanide poisoning. (1.1)

- If clinical suspicion of cyanide poisoning is high, Cyanokit should be administered without delay. (1.2)
- The expert advice of a regional poison control center may be obtained by calling 1-800-222-1222. (1.2)

DOSE AND ADMINISTRATION
- 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. (2.1)
- 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. (2.1)
- The rate of infusion for the second 5 g dose may range from 15 minutes to 2 hours based on patient condition. (2.1)
- The recommended diluent is 0.9% Sodium Chloride injection. (2.2)
- Diluent is not included with Cyanokit. (2.2)
- There are a number of drugs and blood products that are incompatible with Cyanokit, thus Cyanokit requires a separate intravenous line for administration. (2.3)

DOSAGE FORMS AND STRENGTH
Cyanokit consists of 1 vial, containing 5 g lyophilized hydroxocobalamin dark red crystalline powder for injection. (3) After reconstitution, the vial contains hydroxocobalamin for injection, 25 mg/mL. One 5 g vial is a complete starting dose. (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
- Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of alternative therapies, if available. (5.2)
- Allergic reactions may include: anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, and rash. (5.2)
- Blood pressure increase: Substantial increases in blood pressure may occur following Cyanokit therapy. (5.3)

ADVERSE REACTIONS
Most common adverse reactions (>5%) include transient chromaturia, erythema, rash, increased blood pressure, nausea, headache, and injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS contact Meridian Medical Technologies™, Inc. at 1-800-776-3637, 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, treatment of maternal/fetal cyanide poisoning may be lifesaving. (8.1)
- Nursing mothers: Because of the unknown potential for adverse reactions in nursing infants, discontinue nursing after Cyanokit treatment. (8.1)
- No safety and efficacy studies have been performed in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION And FDA-Approved Patient Labeling.

REVISED: 04/2011
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

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

1.2 Identifying Patients with Cyanide Poisoning

Cyanide poisoning may result from inhalation, ingestion, or dermal exposure to various cyanide-containing compounds. Hydroxocobalamin solutions should be visually inspected for particulate matter and color prior to administration. If the reconstituted solution is not dark red or if particulate matter is seen after the solution has been appropriately mixed, the solution should be discarded.

2.1 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.

2.2 Preparation of Solution for Infusion

The 5 g vial of hydroxocobalamin for injection is to be reconstituted 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.

2.3 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).

2.4 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) 5 g 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. Administration of the entire 5 g vial constitutes a complete starting dose. [See How Supplied/Storage and Handling (16) for full kit description.]

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Emergency Patient Management

In addition to Cyanokit, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity. Consideration should be given to decontamination measures based on the route of exposure.

5.2 Allergic Reactions

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of 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 Blood Pressure Increase

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.

5.4 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.

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.
Experience in Healthy Subjects

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
<table>
<thead>
<tr>
<th>ADR</th>
<th>5 g Dose Group</th>
<th>Placebo</th>
<th>10 g Dose Group</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromaturia (red colored urine)</td>
<td>66 (100)</td>
<td>0</td>
<td>18 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>62 (94)</td>
<td>0</td>
<td>18 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Rash*</td>
<td>13 (20)</td>
<td>0</td>
<td>8 (44)</td>
<td>0</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>12 (18)</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (6)</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (6)</td>
<td>1 (5)</td>
<td>6 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte percent decreased</td>
<td>5 (8)</td>
<td>0</td>
<td>3 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>4 (6)</td>
<td>0</td>
<td>7 (39)</td>
<td>0</td>
</tr>
</tbody>
</table>

* 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
- **Immunologic 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.

---

### Table 2

**Laboratory Interference Observed with *In-Vitro* Samples of Hydroxocobalamin**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>No Interference Observed</th>
<th>Artificially Increased</th>
<th>Artificially Decreased</th>
<th>Unpredictable</th>
<th>Duration of Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Chemistry</strong></td>
<td>Calcium</td>
<td>Creatinine</td>
<td>N/A</td>
<td>ALT</td>
<td>24 hours</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
<td>Bilirubin</td>
<td>N/A</td>
<td>Uric Acid AST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potassium</td>
<td>Triglycerides</td>
<td>N/A</td>
<td>CK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloride</td>
<td>Cholesterol</td>
<td>N/A</td>
<td>CKMB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urea</td>
<td>Total protein</td>
<td>N/A</td>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GGT</td>
<td>Glucose</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td>Erythrocytes</td>
<td>Hemoglobin</td>
<td>12 - 16 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematocrit</td>
<td>MCH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCV</td>
<td>MCHC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocytes</td>
<td>Basophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td>aPTT</td>
<td>PT (Quick or INR)</td>
<td>24 - 48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>pH (with all doses)</td>
<td>N/A</td>
<td></td>
<td>48 hours up to 8 days; color changes may persist up to 28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protein</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>erythrocytes</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocytes</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketones</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urobilinogen</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitrite</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urobilinogen</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total protein</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALT</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactate dehydrogenase</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uric Acid</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphate</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloride</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potassium</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥10% interference observed on at least 1 analyzer

Analyzers used: ACL Futura (Instrumentation Laboratory), AxSYM/Architect® (Abbott), BM Coasys® (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.

### 6 ADVERSE REACTIONS

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

### 6.1 Clinical Studies Experience

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.

---

(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.

Based on in-vitro studies and pharmacokinetic data obtained in healthy volunteers, the following table (Table 2) 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. Results may vary substantially from one analyzer to another; therefore, caution should be used when reporting and interpreting laboratory results.
7 DRUG INTERACTIONS
No formal drug interaction studies have been conducted with Cyanokit.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C. There are no adequate and well controlled studies of Cyanokit in pregnant women. In animal studies, hydroxocobalamin caused skeletal and visceral (soft tissue) abnormalities at exposures (based on AUC) similar to human exposures at the therapeutic dose. Cyanokit should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because cyanide readily crosses the placenta, maternal cyanide poisoning results in fetal cyanide poisoning. Timely treatment of the pregnant mother may be lifesaving for both mother and fetus.

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 dependant 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.

8.2 Labor and Delivery
The effect of Cyanokit on labor and delivery is unknown.

8.3 Nursing Mothers
It is not known whether hydroxocobalamin is excreted in human milk. Cyanokit may be administered in life-threatening situations, and therefore, breast-feeding is not a contraindication to its use. Because of the unknown potential for adverse reactions in nursing infants, the patient should discontinue nursing after receiving Cyanokit.

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. Oxalate crystals have been observed in the urine of both healthy subjects given hydroxocobalamin and patients treated with hydroxocobalamin following suspected cyanide poisoning.

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. Hemo dialysis 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 d花dihydroxide dihydrogen phosphate (ester), mono (inner salt), 3'-ester with ether. Hydroxocobalamin has a molecular weight of 1346.36 atomic mass units, an empirical formula of C_62H_89CoN_13O_15P and the following structural formula:

Cyanokit (hydroxocobalamin for injection) 5 g 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 hydroxoglycid 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.

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 hydroxoglycid. The low molecular weight cobalamin-(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 were 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. The predominant 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.

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.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

The effect of hydroxocobalamin on fertility has not been evaluated.

13.2 Animal Pharmacology

Evidence of the effectiveness of hydroxocobalamin for treatment of cyanide poisoning was obtained primarily from studies in animals due to the ethical considerations of performing such controlled studies in humans. While the results of these animal studies 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 Cmax of hydroxocobalamin (total cobalamin-(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>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle N=17</th>
<th>Cyanokit N=19</th>
<th>Cyanokit N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival at Hour 4, n (%)</td>
<td>7 (41)</td>
<td>18 (95)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Survival at Day 14, n (%)</td>
<td>3 (18)</td>
<td>15 (79)</td>
<td>18 (100)</td>
</tr>
</tbody>
</table>

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 CLINICAL STUDIES

Due to ethical considerations, no controlled human efficacy studies have been performed. A controlled animal study demonstrated efficacy in cyanide-poisoned adult dogs [see Animal Pharmacology (13.2)].

14.1 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. Eighteen subjects treated with hydroxocobalamin did not survive. 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, psychosis, 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.

14.2 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 concentrations were 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.

14.3 Cross-Study Findings

Experience with Dosing Greater than 10 g of Hydroxocobalamin

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 11704-370-01) consists of the following:

- One 250 mL glass vial, containing lyophilized hydroxocobalamin for injection, 5 g
- One sterile transfer spike
- One sterile transfer inserter
- 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 40°C (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.

17.1 Erythema and Chromaturia

Patients should be advised 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.

17.2 Rash

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

17.3 Pregnancy and Breast Feeding

Patients should be advised that maternal cyanide poisoning results in fetal cyanide poisoning. Treatment for cyanide poisoning may be lifesaving for both mother and fetus. Patients should notify their physician if they were pregnant during therapy with Cyanokit [see USE IN SPECIFIC POPULATIONS (8.1)]. It is not known whether hydroxocobalamin is excreted in human milk.
Cyanokit (hydroxocobalamin for injection) 5 g for intravenous infusion

Treatment for known or suspected cyanide poisoning

What is Cyanokit?

Cyanokit is an emergency treatment (antidote) used in patients with 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

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.

Cyanokit was approved for the treatment of known or suspected cyanide poisoning based on testing:
- how well it worked in animals (It is not ethical to poison people with cyanide in order to test a treatment.)
- its safety in people with cyanide poisoning

How is Cyanokit used?

Cyanokit is given through a vein (intravenous) over 15 minutes by an emergency care provider or doctor. A second dose may be given to you if needed.

What are possible side effects with Cyanokit?

Serious side effects may include:
- **allergic reactions** Signs of a serious allergic reaction include chest tightness, trouble breathing, swelling, hives, itching, and a rash.
- **increased blood pressure**

Other side effects may include:
- **red colored urine**
- **red colored skin and mucous membranes, acne-like rash**
- **nausea, vomiting, diarrhea, bloody stools, trouble swallowing, stomach pain**
- **throat tightness, dry throat**
- **headache, dizziness, memory problems, restlessness**
- **infusion site reaction**
- **eye swelling, irritation, or redness**
- **swelling of feet and ankles**
- **irregular heart beat, increased heart rate**
- **fluid in lungs**

These are not all the side effects with Cyanokit.

After treatment with Cyanokit:

- **Skin and urine redness.** Skin redness may last up to 2 weeks. Avoid sun exposure while your skin is red. Urine redness may last up to 5 weeks.
- **Acne-like rash.** An acne-like rash may appear 7 to 28 days after treatment with Cyanokit. This rash usually goes away without any treatment.
- **Pregnancy.** Be sure to tell your doctor immediately if you were pregnant or think you may have been pregnant during treatment with Cyanokit. Treatment for cyanide poisoning may save your life and the life of your unborn baby.
- **Breastfeeding.** Talk to your doctor if you breastfeed your child. The ingredient in Cyanokit may pass into your breast milk.

Talk to your doctor about any side effect that bothers you or that does not go away.

Manufactured by:
Merck Santé s.a.s.,
Semoy, France

Distributed by
Meridian Medical Technologies™, Inc.
Columbia, MD 21046
1-800-776-3637

836-2