Full Starting Dose
in a Single Vial

Combating Another Side of Smoke

Cyanide Poisoning and How to Treat It Using the Single-Vial CYANOKIT® 5 g (hydroxocobalamin for injection)

MERIDIAN
MEDICAL TECHNOLOGIES™

CYANOKIT® 5 g
(hydroxocobalamin for injection)

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Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

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

Please see full Prescribing Information for CYANOKIT®.

Important Safety Information (cont'd)

Substantial increases in blood pressure may occur following CYANOKIT® therapy. 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%) are transient and include chromaturia, erythema, rash (predominantly acneiform), increased blood pressure, nausea, headache, decreased lymphocyte percentage, and injection site reactions.

Please see full Prescribing Information for CYANOKIT®.

Identifying Cyanide Poisoning

A hidden threat in some closed-space fires

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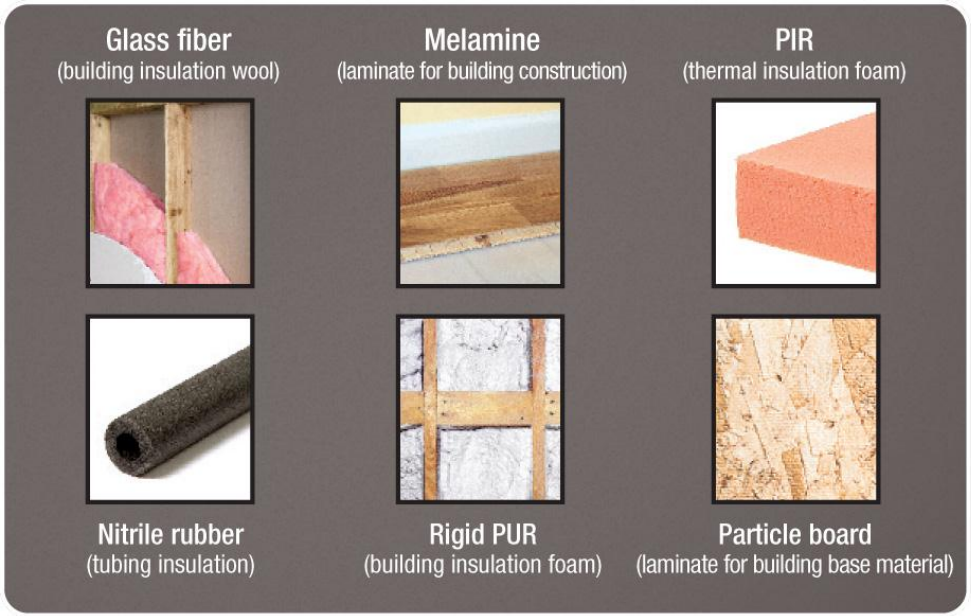
CYANOKIT® 5 g
(hydroxocobalamin for injection)

Cyanide Is an Often Unrecognized Danger in Some Closed-Space Fires

Common Building Materials Known to Release High Levels of Cyanide During Combustion*[1]



*Items pictured may not be accurate representations.

- Cyanide (CN) can be released by virtually any material containing carbon and nitrogen when burned under high temperature and low oxygen conditions[2]
- There is potential for CN toxicity due to the increased use of synthetic materials that produce CN during combustion in closed-space fires[2,3]

Important Note

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.

1. Hertzberg T, Blomqvist P, Dalene M, Skarping G. *Particles and Isocyanates From Fires*. Borås, Sweden: SP Swedish National Testing and Research Institute; 2005:1-51. **2.** Agency for Toxic Substances and Disease Registry. Cyanide toxicity. *Am Fam Physician*.1993;48(1):107-114. **3.** Alcorta R. Smoke inhalation & acute cyanide poisoning. In: Losavio K, ed. *Smoke Inhalation & Hydrogen Cyanide Poisoning*. San Diego, CA: JEMS Communications; 2004:6-17.

Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Difficult to Diagnose, Easy to Suspect

Distinguishing between cyanide and carbon monoxide poisoning can be difficult

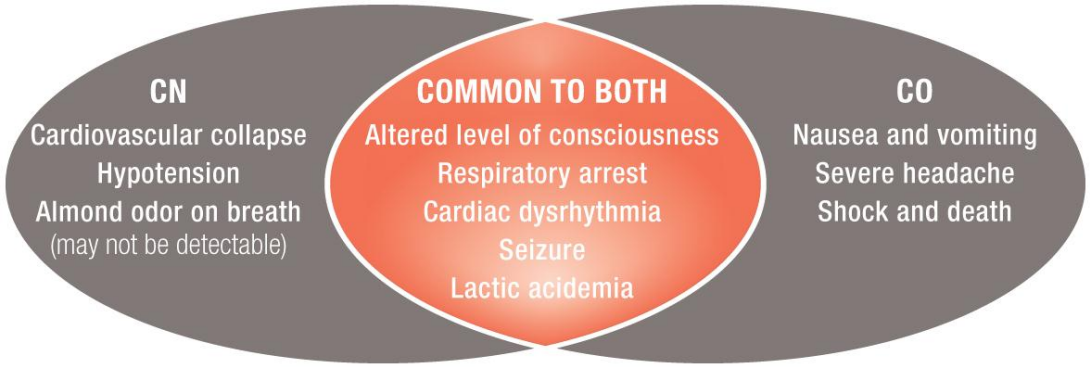
BECAUSE…

- Many symptoms of cyanide (CN) and carbon monoxide poisoning are common to both or very similar,[1] *and*
- There is no diagnostic test to confirm or distinguish cyanide poisoning from carbon monoxide poisoning in the field[1]

CYANIDE POISONING…

- Should be suspected in any person exposed to smoke in a closed-space fire,[1,3] *and*
- When suspicion of cyanide poisoning is high, an antidote should be considered for empiric treatment[1,3]

Moderate to Severe Poisoning Signs/Symptoms[1,2]



1. O'Brien DJ, Augustine J, Walsh DW. Cyanide exposure, smoke inhalation, and pre-hospital treatment: recognizing the signs and symptoms and available treatment options. In: *Smoke: Cyanide and Carbon Monoxide: The Toxic Twins of Smoke Inhalation*. Cyanide Poisoning Treatment Coalition: Indianapolis, IN: 2009:20-24. **2.** Lawson-Smith P, Jansen EC, Hyldegaard O. Cyanide intoxication as part of smoke inhalation—a review on diagnosis and treatment from the emergency perspective. *Scand J Trauma Resusc Emerg Med*. 2011;19:1-5. **3.** Eckstein M, Maniscalco PM. Focus on smoke inhalation—the most common cause of acute cyanide poisoning. *Prehosp Disaster Med*. 2006;21(2):s49-s55.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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When to Suspect Cyanide Poisoning*[1,2]

Cyanide poisoning in smoke-inhalation victims should be suspected if the following manifestations are present*[1,2]:

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

*List may not be comprehensive.

Important Note

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

1. Eckstein M, Maniscalco PM. Focus on smoke inhalation—the most common cause of acute cyanide poisoning. *Prehosp Disaster Med*. 2006;21(2):s49-s55.
2. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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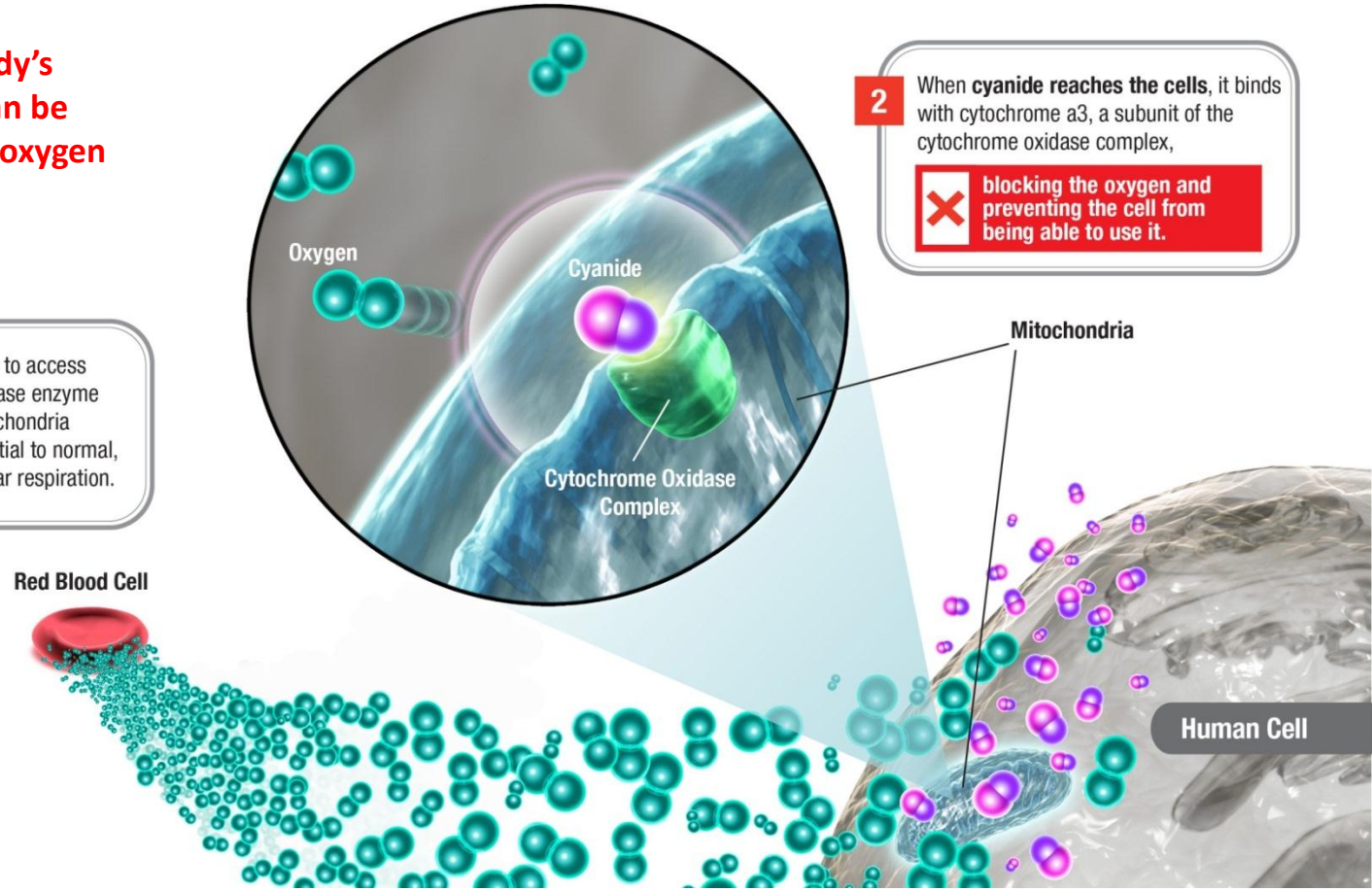
How Cyanide Affects Cellular Respiration

Cyanide may disable the body's ability to use oxygen so it can be fatal despite the amount of oxygen available to the body.[1,2]



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011. **2.** Schnepp 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; 2009:3-8.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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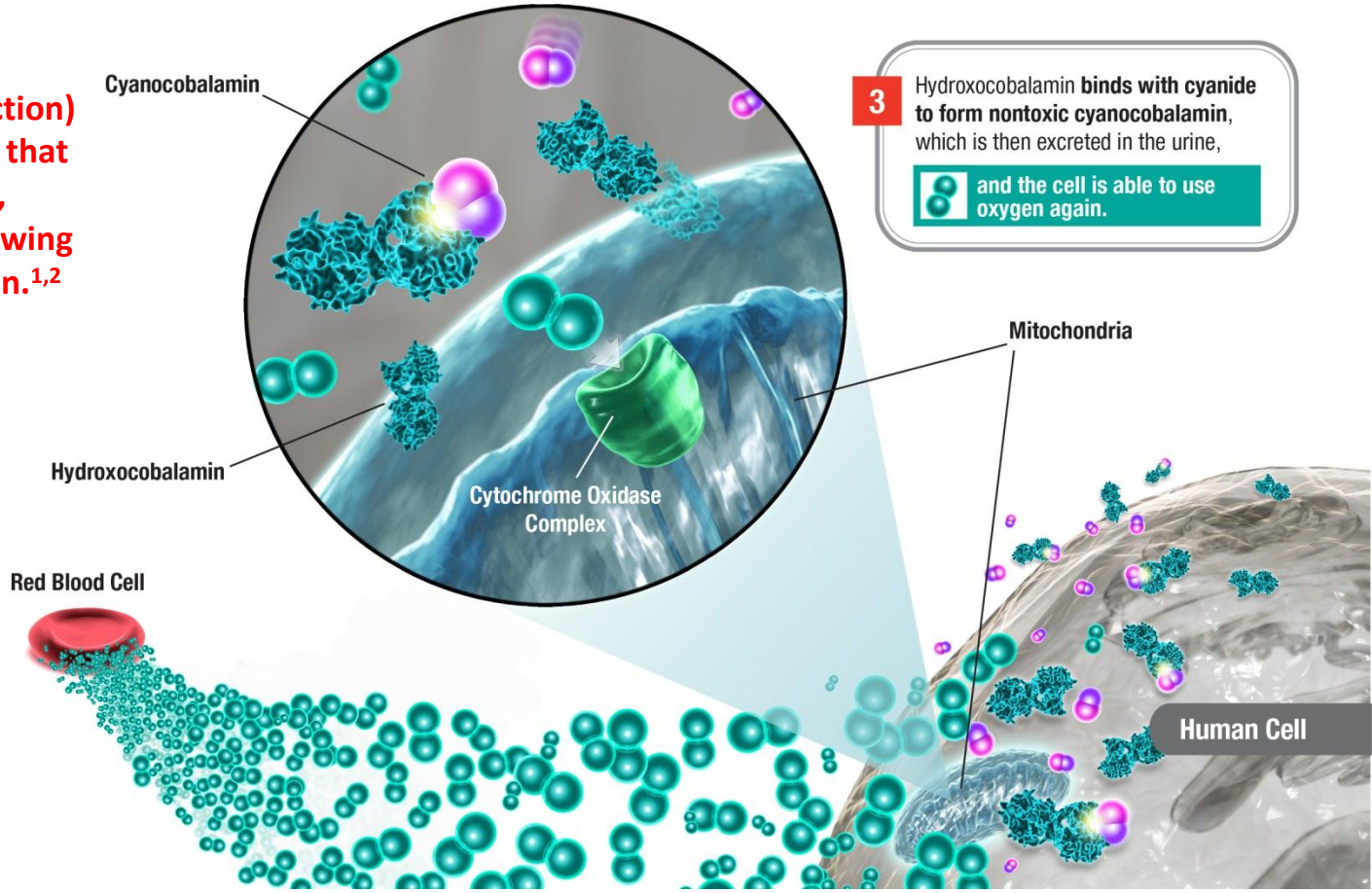
How Hydroxocobalamin Interacts With Cyanide

CYANOKIT® 5 g (hydroxocobalamin for injection) is the only cyanide antidote that contains hydroxocobalamin, which binds to cyanide, allowing the body to use oxygen again.[1,2]



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011. **2.** Schnepp 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; 2009:3-8.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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CYANOKIT® 5 g
(hydroxocobalamin for injection)

FDA-approved for the treatment of known or suspected cyanide poisoning.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

Indication[1]

- CYANOKIT® 5 g (hydroxocobalamin for injection) 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

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.

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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For Known or *Suspected* Cyanide Poisoning[1]

- It has been shown that the concentration of blood lactate increases proportionally with the severity of cyanide (CN) poisoning and that hydroxocobalamin treatment results in rapid resolution of CN-induced lactic acidemia[1-3]
- Studies have shown CYANOKIT® 5 g (hydroxocobalamin for injection) to be generally well-tolerated even in the absence of cyanide poisoning[4-7]
- Has been used in France since 1996 and in the U.S. since 2007 to treat suspected or known cyanide poisoning[8]

Important Safety Information

Substantial increases in blood pressure may occur following CYANOKIT® therapy. 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.

1. Lawson-Smith P, Jansen EC, Hyldegaard O. Cyanide intoxication as part of smoke inhalation—a review on diagnosis and treatment from the emergency perspective. *Scand J Trauma Resusc Emerg Med*. 2011;19:1-5. 10. **2.** Baud FJ, Borron SW, Mégarbane B, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Me*d. 2002;30(9):2044-2050. **3.** Torres EC, Bustamante RS, Granizo EG, et al. Hydroxocobalamin and lactate concentration in patients suspected of having cyanuric acid poisoning related to smoke inhalation syndrome. *Emergencias*. 2010;22:9-14. **4.** Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011. **5.** Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C. Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Ann Emerg Med*. 2007;49(6):794-801. **6.** Borron SW, Baud FJ, Mégarbane B, Bismuth C. Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. *Am J Emerg Med*. 2007;25(5):551-558. **7.** Fortin JL, Giocanti JP, Ruttimann M, Kowalski JJ. Prehospital administration of hydroxocobalamin for smoke inhalation-associated cyanide poisoning: 8 years of experience in the Paris Fire Brigade. *Clin Toxicol (Phila).* 2006;44(suppl 1):37-44. **8.** Borron SW. Recognition and treatment of acute cyanide poisoning. *J Emerg Nurs.* 2006;32(4 suppl):s12-s18.

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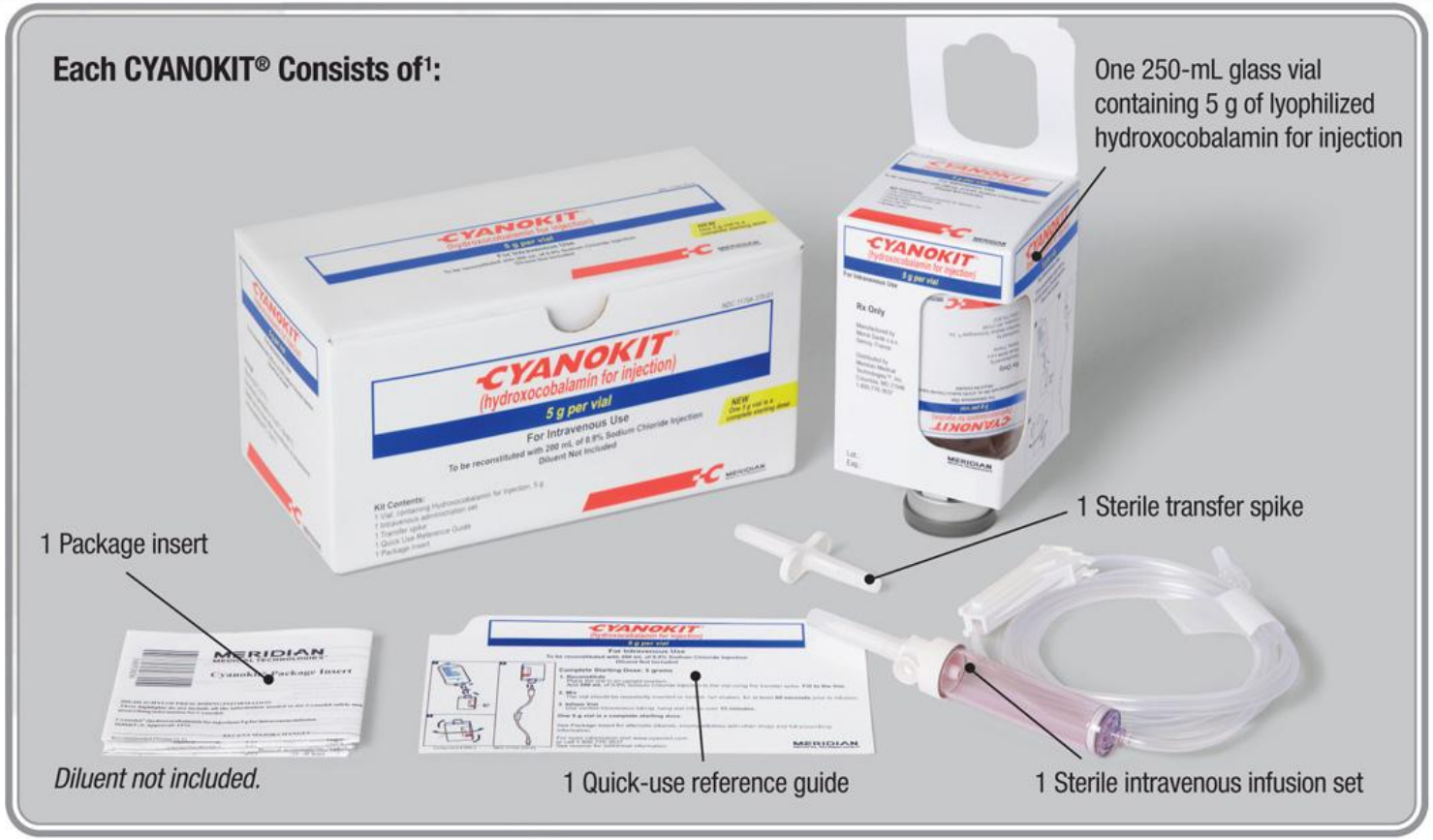
CYANOKIT® 5 g (hydroxocobalamin for injection)

Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Contents of Single-Vial CYANOKIT® 5 g (hydroxocobalamin for injection)[1]



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Compared to the Two-Vial Version…

The Single-Vial CYANOKIT® (hydroxocobalamin for injection) 5 g Features:

- The full starting dose in a single vial
- A longer shelf life from the date of formulation
- More compact packaging

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Recommended Dosing[1]

- The starting dose of CYANOKIT® 5 g (hydroxocobalamin for injection) for adults is 5 g
  - One 5-g vial
  - Administer by intravenous (IV) infusion over 15 minutes
- Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by IV infusion up to a total dose of 10 g
  - The rate of infusion for a potential second dose may range from 15 minutes (for patients in extremis) to 2 hours, as clinically indicated

Important Safety Information

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Allergic reactions may include anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, rash, and angioneurotic edema. Substantial increases in blood pressure may occur following treatment with CYANOKIT®.

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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How to Administer Single-Vial CYANOKIT® 5 g

(hydroxocobalamin for injection)

Prepare and administer in 3 steps.

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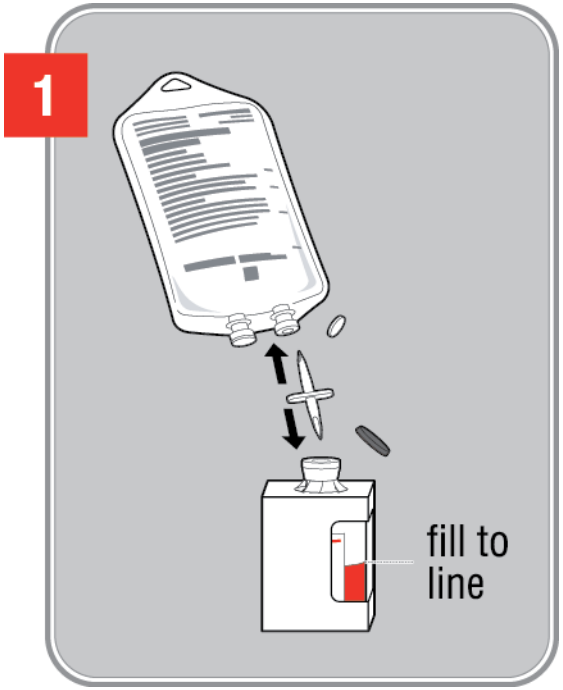
CYANOKIT® 5 g (hydroxocobalamin for injection)

Step 1: RECONSTITUTE[1]

- Place the vial in an upright position
- Add **200 mL** of 0.9% Sodium Chloride Injection to the vial using the sterile transfer spike. **Fill to the line.**
  - 0.9% Sodium Chloride Injection is the recommended diluent
  - Diluent is not included in the kit
  - Lactated Ringer's Solution and 5% Dextrose Injection have also been found to be compatible with hydroxocobalamin



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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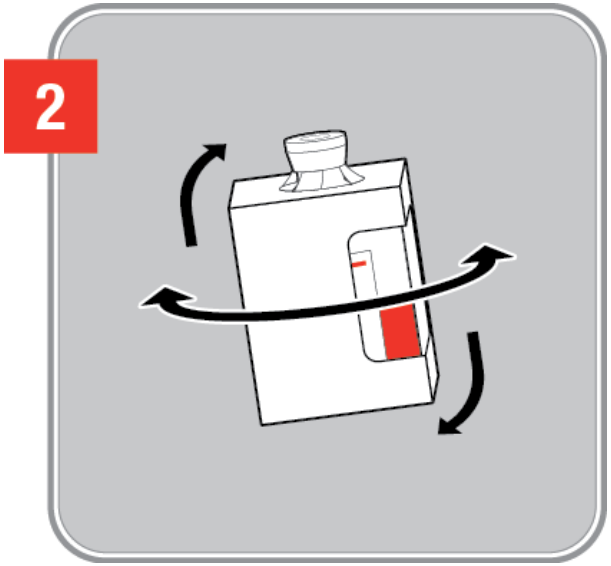
Step 2: MIX[1]

- The vial should be repeatedly inverted or rocked, not shaken, for at least **60 seconds** prior to infusion



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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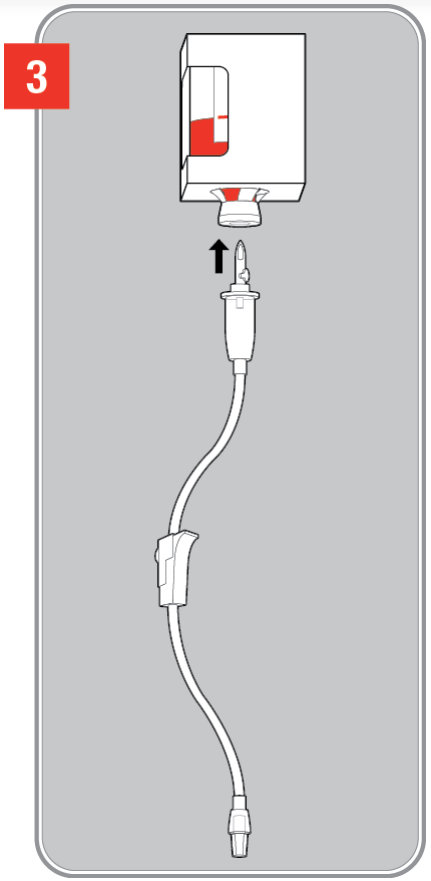
Step 3: INFUSE VIAL[1]

- Use vented intravenous tubing
- Hang and infuse over **15 minutes**

One 5-g vial is a complete starting dose.



1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Considerations During Administration[1]

- **Inspect CYANOKIT® 5 g (hydroxocobalamin for injection) solution** for particulate matter and color prior to administration
  - Discard if particulate matter is present
  - Discard if solution is not dark red
- **Use a separate IV line** for infusion
  - A separate line is required as a number of drugs used in resuscitation efforts are incompatible with CYANOKIT®
- **Use caution** when administering other cyanide antidotes simultaneously with CYANOKIT®
  - If the decision is made to administer another antidote, do not use the same IV line

Important Safety Information

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.

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Storing and Stocking CYANOKIT® 5 g

(hydroxocobalamin for injection)

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CYANOKIT® 5 g (hydroxocobalamin for injection)

Storage of **Lyophilized** Form[1]

- CYANOKIT® 5 g (hydroxocobalamin for injection) should be stored at 25°C (77°F)
  - Excursions are permitted to 15° to 30°C (59° to 86°F)
- CYANOKIT® may be exposed, during short periods, to temperature variations of usual transport, transport in the desert, and freezing/defrosting cycles
  - Usual transport defined as 15 days subjected to temperatures ranging from 5° to 40°C (41° to 104°F)
  - Transport in the desert defined as 4 days subjected to temperatures ranging from 5° to 60°C (41° to 140°F)
  - Freezing/defrosting cycles defined as 15 days subjected to temperatures ranging from –20° to 40°C (–4° to 104°F)

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Storage of **Reconstituted** Drug Product[1]

- CYANOKIT® 5 g (hydroxocobalamin for injection) may be kept up to 6 hours at a temperature not exceeding 40°C (104°F)
- Do not freeze
- Product not used by 6 hours should be discarded

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Prehospital Stocking

- Reasons to consider stocking CYANOKIT® 5 g (hydroxocobalamin for injection) directly on first responder vehicles:
  - Existence of cyanide in fire smoke from closed-space fires[1]
  - Toxic threat cyanide presents to fire victims as well as firefighters[1,2]
    - Death can occur within minutes of exposure to moderate to high concentrations of cyanide[1]
  - Apparent low risk of causing harm by administering hydroxocobalamin for prehospital empiric treatment of smoke inhalation-associated cyanide poisoning[1]

Important Safety Information

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Allergic reactions may include anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, rash, and angioneurotic edema. Substantial increases in blood pressure may occur following treatment with CYANOKIT®.

1. Eckstein M, Maniscalco PM. Focus on smoke inhalation—the most common cause of acute cyanide poisoning. *Prehosp Disaster Med*. 2006;21(2):s49-s55. **2.** Walsh DW, Eckstein M. Hydrogen cyanide in fire smoke: an underappreciated threat. *Emerg Med Serv*. 2004;33(10):160-163.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Hospital Stocking

- It has been recommended by an expert panel of physicians for consensus guidelines for stocking antidotes that hydroxocobalamin be stocked in the emergency department[1]
  - It must be available immediately because the administration of a cyanide antidote can resuscitate a patient only of it is given before irreversible injury develops[1]

Important Safety Information

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.

1. Dart RC, Borron SW, Caravati EM, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med.* 2009;54:386-394.

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Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Grant Information

Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Grant Eligibility

- CYANOKIT® 5 g (hydroxocobalamin for injection) is approved on the Department of Homeland Security's Authorized Equipment List (AEL), making it eligible for the following grant programs[1]:
  - State Homeland Security Program (SHSP)
  - Urban Area Security Initiative (UASI)
  - Metropolitan Medical Response System (MMRS)
  - Transit Security Grant Program (TSGP)
- Additional grant information and resources can be found at:
  - emsgrantshelp.com
  - firegrantshelp.com
  - usfa.dhs.gov/grants
  - fema.gov/firegrants/
  - usfa.dhs.gov/fireservice/grants/afgp

These Web sites are neither owned nor controlled by Meridian. Meridian is not responsible for the content or services of these sites.

1. Department of Homeland Security. Authorized equipment list. https://www.rkb.us/mel.cfm?subtypeid=549. Accessed September 2, 2011.

Please see Important Safety Information on slide 3 and full Prescribing Information for CYANOKIT® on slide 35.

Questions?

For more information about CYANOKIT® 5 g (hydroxocobalamin for injection):

Call 1-800-638-8093

or

Visit CYANOKIT.com

For medical questions concerning CYANOKIT® call 1-800-438-1985, Monday through Friday, 8:00 am to 8:00 pm EST.

To report an adverse event or speak to a member of Pfizer U.S. Medical Information, call 1-800-438-1985.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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Cyanide Poisoning[1,2]

SUSPECT IT.*

Cyanide poisoning in smoke-inhalation victims should be suspected if the following manifestations are present*[1,2]:

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

*List may not be comprehensive.

Cyanide poisoning should be suspected.

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.

1. Eckstein M, Maniscalco PM. Focus on smoke inhalation—the most common cause of acute cyanide poisoning. *Prehosp Disaster Med*. 2006;21(2):s49-s55.
2. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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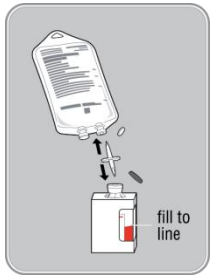
Cyanide Poisoning[1]

TREAT IT.

Prepare and administer CYANOKIT® 5 g (hydroxocobalamin for injection) in 3 steps[1]:

1. Reconstitute

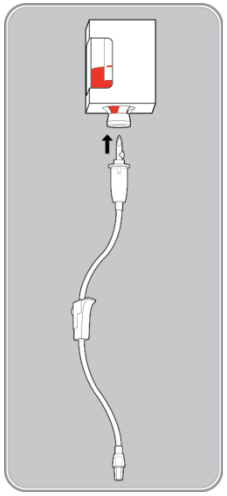


Place the vial in an upright position. Add **200 mL** of 0.9% Sodium Chloride Injection to the vial using the transfer spike. **Fill to the line.**

2. Mix

The vial should be repeatedly inverted or rocked, not shaken, for at least **60 seconds** prior to infusion.

3. Infuse vial



Use vented intravenous tubing, hang and infuse over **15 minutes**.

1. Cyanokit (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2011.

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CYANOKIT® 5 g (hydroxocobalamin for injection)

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

Please see full Prescribing Information for CYANOKIT®.

►Click for Table of Contents

Important Safety Information (cont'd)

Substantial increases in blood pressure may occur following CYANOKIT® therapy. 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%) are transient and include chromaturia, erythema, rash (predominantly acneiform), increased blood pressure, nausea, headache, decreased lymphocyte percentage, and injection site reactions.

Please see full Prescribing Information for CYANOKIT®.

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MERIDIAN MEDICAL TECHNOLOGIES™

CYANOKIT® 5 g (hydroxocobalamin for injection)

Prescribing Information for CYANOKIT® 5 g
(hydroxocobalamin for injection)

MERIDIAN MEDICAL TECHNOLOGIES™

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CYANOKIT® 5 g
(hydroxocobalamin for injection)

MERIDIAN MEDICAL TECHNOLOGIES™

10053836

Cyanokit® Package Insert

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

----------RECENT MAJOR CHANGES ----------

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)

----------DOSAGE 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 (for patients in extremis) 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 (hydroxocobalamin for injection) 5 g for intravenous infusion 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.
- 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: CONTENTS*

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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, 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. If clinical suspicion of cyanide poisoning is high, Cyanokit should be administered without delay.

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.

The expert advice of a regional poison control center may be obtained by calling 1-800-222-1222.

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.

1.3 Use with Other Cyanide Antidotes

Caution should be exercised when administering other cyanide antidotes simultaneously with Cyanokit, as the safety of co-administration 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 (2.3).]*

2 DOSAGE AND ADMINISTRATION

Comprehensive treatment of acute cyanide intoxication requires support of vital functions. Cyanokit should be administered in conjunction with appropriate airway, ventilatory and circulatory support.

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. 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.

2.2 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.

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.

2.3 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

(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.

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 Coasys110 (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.

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 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
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.

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

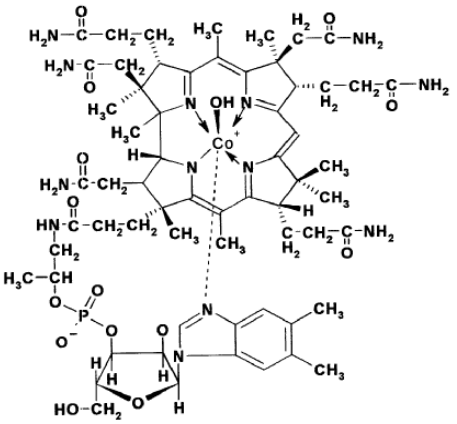
The safety and effectiveness of Cyanokit have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

No data are available about overdose with Cyanokit in adults. Should overdose occur, treatment should be directed to the management of symptoms. 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. 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) 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 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.

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 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 cobalamins-(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 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 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. 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.

14.2 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 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.

14.3 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 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.

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 acneiform 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.

17.4 FDA-Approved Patient Labeling

Patient Information
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
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