

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-041**

**MEDICAL REVIEW(S)**



FDA, Center for Drug Evaluation and Research,  
Division of Anesthesia, Analgesia and Rheumatology Products

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**CLINICAL REVIEW**

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Established Name: Hydroxocobalamin lyophilized powder for injection  
(Proposed) Trade Name: Cyanokit  
Therapeutic Class: antidote

Applicant: EMD Pharmaceuticals, Inc.  
Priority Designation: P

Formulation: lyophilized powder

Dosing Regimen: 5.0 gram IV infusion over 15 minutes

Indication: treatment of known or suspected acute cyanide  
poisoning

Intended Population: adult cyanide-poisoning victims

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## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY.....</b>	<b>5</b>
1.1	RECOMMENDATION ON REGULATORY ACTION .....	7
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS .....	8
1.2.1	Risk Management Activity .....	8
1.2.2	Required Phase-4 Commitments.....	8
1.2.3	Other Phase 4 Requests.....	10
1.3	SUMMARY OF CLINICAL FINDINGS .....	10
1.3.1	Brief Overview of Clinical Program.....	10
1.3.2	Efficacy.....	11
1.3.3	Safety .....	12
1.3.4	Dosing Regimen and Administration.....	14
1.3.5	Drug-Drug Interactions.....	14
1.3.6	Special Populations.....	14
<b>2</b>	<b>INTRODUCTION AND BACKGROUND .....</b>	<b>15</b>
2.1	PRODUCT INFORMATION .....	15
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	15
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES .....	15
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	16
2.5	PRESUBMISSION REGULATORY ACTIVITY .....	16
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	20
<b>3</b>	<b>SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES .....</b>	<b>21</b>
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....	21
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY .....	21
<b>4</b>	<b>DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....</b>	<b>23</b>
4.1	SOURCES OF CLINICAL DATA .....	23
4.2	TABLES OF CLINICAL STUDIES .....	23
4.3	REVIEW STRATEGY .....	23
4.4	DATA QUALITY AND INTEGRITY .....	24
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	24
4.6	FINANCIAL DISCLOSURES.....	24
<b>5</b>	<b>CLINICAL PHARMACOLOGY .....</b>	<b>26</b>
5.1	PHARMACOKINETICS .....	26
5.2	PHARMACODYNAMICS.....	26
5.3	EXPOSURE-RESPONSE RELATIONSHIPS .....	26
<b>6</b>	<b>INTEGRATED REVIEW OF EFFICACY .....</b>	<b>28</b>
6.1	INDICATION.....	28
6.1.1	Methods .....	28
6.1.2	General Discussion of Endpoints.....	28
6.1.3	Study Design.....	28
6.1.4	Efficacy Findings.....	29
6.1.5	Clinical Microbiology.....	30
6.1.6	Efficacy Conclusions .....	30
<b>7</b>	<b>INTEGRATED REVIEW OF SAFETY .....</b>	<b>31</b>
7.1	METHODS AND FINDINGS .....	31
7.1.1	Deaths .....	32

7.1.2	Other Serious Adverse Events .....	34
7.1.3	Dropouts and Other Significant Adverse Events .....	35
7.1.4	Other Search Strategies.....	39
7.1.5	Common Adverse Events .....	39
7.1.6	Less Common Adverse Events .....	43
7.1.7	Laboratory Findings.....	44
7.1.8	Vital Signs .....	54
7.1.9	Electrocardiograms (ECGs).....	57
7.1.10	Immunogenicity .....	58
7.1.11	Human Carcinogenicity .....	58
7.1.12	Special Safety Studies.....	58
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	59
7.1.14	Human Reproduction and Pregnancy Data .....	59
7.1.15	Assessment of Effect on Growth .....	59
7.1.16	Overdose Experience .....	60
7.1.17	Postmarketing Experience .....	60
7.2	<b>ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS .....</b>	<b>61</b>
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety .....	61
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	63
7.2.3	Adequacy of Overall Clinical Experience .....	64
7.2.4	Adequacy of Special Animal and/or In Vitro Testing .....	64
7.2.5	Adequacy of Routine Clinical Testing.....	64
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup.....	65
7.2.7	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study .....	65
7.2.8	Assessment of Quality and Completeness of Data .....	65
7.2.9	Additional Submissions, Including Safety Update .....	65
7.3	<b>SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....</b>	<b>66</b>
7.4	<b>GENERAL METHODOLOGY .....</b>	<b>66</b>
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence.....	66
7.4.2	Explorations for Predictive Factors .....	67
7.4.3	Causality Determination .....	68
<b>8</b>	<b>ADDITIONAL CLINICAL ISSUES .....</b>	<b>69</b>
8.1	DOSING REGIMEN AND ADMINISTRATION .....	69
8.2	DRUG-DRUG INTERACTIONS .....	69
8.3	SPECIAL POPULATIONS.....	70
8.4	PEDIATRICS .....	70
8.5	ADVISORY COMMITTEE MEETING .....	70
8.6	LITERATURE REVIEW .....	70
8.7	POSTMARKETING RISK MANAGEMENT PLAN .....	71
8.8	OTHER RELEVANT MATERIALS .....	72
<b>9</b>	<b>OVERALL ASSESSMENT.....</b>	<b>73</b>
9.1	CONCLUSIONS .....	73
9.2	RECOMMENDATION ON REGULATORY ACTION .....	73
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS .....	74
9.3.1	Risk Management Activity .....	74
9.3.2	Required Phase 4 Commitments .....	75
9.3.3	Other Phase 4 Requests.....	76
9.4	LABELING REVIEW.....	76
9.5	COMMENTS TO APPLICANT.....	77

<b>10</b>	<b>APPENDICES .....</b>	<b>78</b>
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS .....	78
10.1.1	Study: EML 015722-H101 .....	78
10.1.2	Baud-1 Study .....	90
10.1.3	Baud-2 Study .....	98
10.1.4	Baud-3 Study .....	104
10.1.5	Fortin Study .....	111
10.2	LINE-BY-LINE LABELING REVIEW.....	119
10.3	ADVERSE EVENTS .....	134
10.4	INFORMATION ON PATIENT DEATHS.....	144
10.5	REFERENCES .....	166

## 1 EXECUTIVE SUMMARY

Cyanokit consists of two glass containers, each holding 2.5 g of lyophilized hydroxocobalamin (OH-Co), as well as a transfer spike for reconstituting the drug product and intravenous tubing system. Each container is intended to be filled with 100 mL of sterile saline for injection and administered intravenously over a period of 7.5 minutes. The Sponsor proposes that a 5-g dose of OH-Co administered over 15 minutes is indicated for the treatment of known or suspected cyanide toxicity in adults.

As an antidote to cyanide poisoning, Cyanokit provides several advantages over the products currently marketed in this country: Cyanide Antidote Kit® (Bedford Pharmaceuticals) and Cyanide Antidote Package® (Akorn Inc.).

1. Cyanokit requires the administration of a single drug product, OH-Co, compared to the sequential administration of amyl nitrite, sodium nitrite and sodium thiosulfate.
2. The mechanism of action for Cyanokit does not involve inducing a condition that imposes additional risk for patients. Amyl and sodium nitrite work, in part, by producing methemoglobinemia as a means of removing cyanide ions from the circulation.
3. The development program for Cyanokit included a well-controlled animal studies conducted under Good Laboratory Practices Guidelines, a placebo-controlled, safety and tolerability study in healthy volunteers, and several studies examining its use in French patients. This level of evaluation provided data for a better delineation of the risks, benefits, and dosing requirements than is currently available for the other marketed products, thereby allowing for more comprehensive labeling and potentially safer use.

The development plan, as alluded to above, included multiple animal and human studies. The two studies on which the recommendation of regulatory action relies most heavily are the animal efficacy study conducted in dogs and the safety and tolerability study conducted in healthy volunteers.

The dog study involved the administration of potassium cyanide intravenously until the animals were apneic for three minutes, at which time, the cyanide infusion was stopped, study drug administration was begun and the animals were mechanically ventilated. At two weeks after the poisoning and treatment, 18% of the animals in the placebo arm (vehicle in normal saline) survived; whereas, 79% and 100% of the animals treated with 75 mg/kg and 150 mg/kg OH-Co, respectively, survived. These OH-Co doses correspond to 5-g and 10-g dosing in a 70-kg human.

The healthy volunteer study of safety and tolerability assessed the risks associated with receiving OH-Co in the absence of cyanide exposure. This study was important for two reasons: it allowed a risk assessment for patients who may be treated for suspected cyanide toxicity, when in fact, they were not exposed to cyanide, and it provided a basis on which to assess the adverse events which occurred in patients treated for known or suspected cyanide poisoning in the uncontrolled French studies of Cyanokit use. This study indicated that the major risk was dose-dependent hypertension which began shortly after the HO-Co infusion was initiated and resolved hours

after it was completed. Elevations in both diastolic and systolic blood pressures were observed and were reported to be as high as 40 and 90 mmHg, respectively, over baseline measurements. For victims of cyanide poisoning, hypotension and shock are typical occurrences, and for these patients, the hypertensive effect of OH-Co is potentially beneficial. For non-cyanide exposed patients, the elevation in blood pressure could be an early indication that the toxicity is due to other causes. In addition to hypertension, the most common adverse events included rashes, allergic type reactions and an intense reddening of the skin and urine – all of which developed shortly after infusion of the drug was begun.

The level of efficacy in the animal study and the tolerability observed in the human study for the 5-g dose of OH-Co provide a favorable benefit-risk ratio. The additional increase in survival seen at the higher OH-Co dose, suggests that those patients who respond incompletely to treatment with a 5-g dose may benefit from additional dosing, up to 10 g, provided they are carefully monitored for untoward blood pressure changes and possible allergic reactions.

The preliminary results of the human and animal studies raised three important concerns that the Agency asked the Sponsor to address during product development. These included:

1. assessment of the risk associated with exposure to high levels of cyanocobalamin, which would result from treatment of toxic doses of cyanide
2. assessment of hypertensive responses to OH-Co in dogs not exposed to cyanide to confirm the animal model adequately mimics human response to the drug
3. assessment of skin reactions to OH-Co in an animal model to characterize the nature of the risk to humans

The Sponsor evaluated the effects of high dose cyanocobalamin in dogs. The study conducted indicated that, in contrast to hydroxocobalamin, cyanocobalamin did not result in hemodynamic changes that differed from placebo. In addition, cyanocobalamin administration did not result in significant toxicity for the doses administered. The dose of cyanocobalamin that could be administered was limited by its low solubility in saline and the maximum fluid volume that could be administered to dogs.

The Sponsor conducted a rabbit study to assess the hypertension observed with administration of OH-Co in humans in the absence of cyanide poisoning. The study demonstrated an increase in blood pressure and systemic vascular resistance that were accompanied by a decrease in cardiac output associated with OH-Co infusions. Further testing suggested that the cardiovascular changes were possibly due to the scavenging of nitric oxide by OH-CO.

In a 3T3-Neutral Red uptake phototoxicity test, hydroxocobalamin was not found to be phototoxic. No changes, other than red coloration, were observed in the animal studies, suggesting the differences observed between humans and dogs are related to differences in skin pigmentation or the lack of sweat glands in dog skin.

In addition to the human safety and tolerability study, the Sponsor secured access to four French studies which documented the use of Cyanokit in the treatment of patients rescued at the scene of a fire and patients exposed to cyanide by sources other than smoke inhalation, primarily by

ingestion in attempts at suicide. None of the studies had a comparator arm, and three of the studies, the Baud-2, Baud-3 and Fortin studies, were retrospective in design. Thus, it is not possible to draw conclusions as to the benefits or risks of Cyanokit treatments; however, the studies, especially the Baud-1 and Baud-3 studies, do provide valuable data suggesting efficacy and allowing a comparison of the adverse events observed in the healthy-volunteer study with those observed for patients with cyanide exposure. Specifically, the Baud-1 and Baud-3 studies assessed blood cyanide levels prior to treatment and were able to demonstrate a substantial number of survivors despite blood cyanide levels in the range generally considered lethal.

### **1.1 Recommendation on Regulatory Action**

It is recommended that an approval action be taken for this NDA.

By means of an animal efficacy study, the Sponsor has demonstrated a survival benefit with the administration of hydroxocobalamin compared to placebo. In this dog study, the two doses of hydroxocobalamin evaluated, 75 and 150 mg/kg, correspond to the proposed 5-g and 10-g doses for adult humans. The lower dose was associated with a 79% survival rate at two weeks post-poisoning; the higher dose resulted in a 100% survival rate. In a study evaluating the effects of hydroxocobalamin administration in the absence of cyanide exposure, the Sponsor demonstrated that the drug product was generally well tolerated at the 5-g dose level. The adverse events observed: hypertension, allergic reactions, and a red coloration of the skin and urine, tended to occur early during administration of the drug product, could be readily monitored and treated if necessary, and were noted to occur less frequently and with less intensity in the 5-g dose group than in the 10-g dose group.

Hydroxocobalamin was given a priority review designation for the following reasons:

- It is indicated for the treatment of cyanide poisoning, a life-threatening condition.
- It offers advantages over the existing treatments:
  - a. It is a single drug product to be infused versus an inhaled product followed by two intravenously infused drugs administered sequentially.
  - b. It forms no toxic intermediary, i.e., methemoglobinemia, that could pose additional risk to patients regardless of cyanide-poisoning status.
  - c. The risk profile has been characterized for patients who have not been exposed to cyanide. The same has not been done for the components of the currently marketed antidote products.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

Hydroxocobalamin does not produce a mind- or mood-altering effect. Therefore, it is not likely to be abused, misused or diverted, and no special postmarketing risk management activities are warranted at this time.

### 1.2.2 Required Phase-4 Commitments

The following Phase-4 commitments are required from a clinical perspective:

1. The Sponsor's obligation under 21 CFR §314 Subpart I to further evaluate safety and efficacy may be fulfilled by the two protocols, titled CRISIS-1 and CRISIS-2, which the Sponsor has submitted. These are designed to evaluate safety and efficacy of standard care and Cyanokit when used to treat victims of smoke inhalation. CRISIS-1 (Cyanide's Role In Smoke Inhalation Study) will evaluate outcomes for patients who were exposed to smoke inhalation prior to approval of Cyanokit and treated with currently available therapies. CRISIS-2 (Cyanokit Rescue In Smoke Inhalation Study) will evaluate outcomes when Cyanokit is used to treat such patients once it is approved.
2. The compatibility of hydroxocobalamin with the most frequently administered resuscitation drugs and blood products should be completed within one year of product approval. This assessment is critical as a single intravenous line is often the only patient access for therapeutic interventions administered by emergency medical personnel. The Sponsor may submit currently available data to partially fulfill this requirement and supplement this information with data obtained from its own studies.

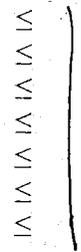
The following Phase-4 requirements are recommended by the Pharmacology-Toxicology team and are considered as requirements by the clinical review team as well:

1. The sponsor should conduct the standard battery of reproductive toxicology studies as described in ICHM3, S5A, S5B, and S5B(M) Guidances to Industry, as follows:
  - a. Segment I (Fertility and Early Embryonic Development)
  - b. Segment II (Embryofetal Development) in two species
  - c. Segment III (Peri- and Post-natal Development)
2. Refer to the Guidances for Industry Q3A (for drug substance) and Q3B(R) (for drug product) for advice on studies required to support the safety of impurities. At a minimum, two genotoxicity studies and one acute single dose animal study with a 14 day follow-up should be conducted. The genotoxicity studies should include a test for mutagenesis and a test for clastogenicity; these may be in vitro studies. The single dose animal study should include sufficient animals of both sexes (n=6 for rodents) and a sufficient range of doses such that, a no or minimal toxicity to frank toxicity is expected. These studies should incorporate at least the highest level of each impurities expected in the drug substance or product (stability).

The following three conditions for approval and two Phase-4 requirements were specified by the Chemistry, Manufacturing and Controls review team and are considered as requirements by the clinical review team as well:

Conditions for approval:

1. Revise the impurity limits (% w/w) in the drug substance hydroxocobalamin as recommended and list the identified impurities (— and —) by their abridged chemical names: **b(4)**

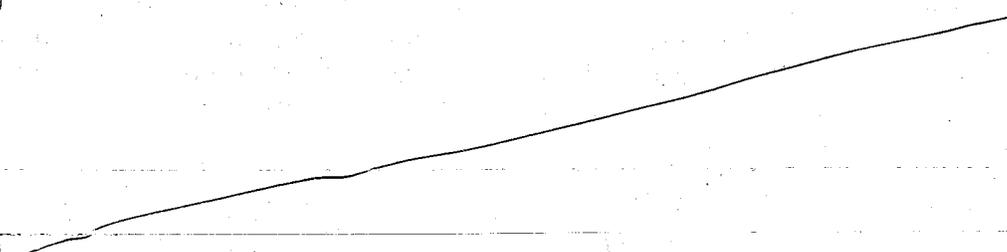
Impurity —, RRT= **b(4)**   
Impurity —, RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Impurity —, RRT= **b(4)**  
Individual drug-related unspecified impurity **b(4)**  
Total (sum of all reportable related impurities ≥ —%) **b(4)**

2. Revise the release and shelf-life impurity limits (% w/w) in the drug product (hydroxocobalamin for injection) as recommended and list the identified impurities (— and —) by their abridged chemical names:

Impurity —, RRT= **b(4)**   
Impurity —, RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Impurity —, RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Impurity at RRT= **b(4)**  
Individual drug-related unspecified impurity **b(4)**  
Total (sum of all reportable related impurities ≥ —%) **b(4)**

3. Explain why all the stability data of Batches 2079, 2080 and 2081 stored at 25°C/60% RH, have identical values for the content of Impurity RRT= — on each time point reported. **b(4)**

Phase-4 Commitments:

1. **b(4)**
- 

2. By June 30, 2007, the following additional data should be submitted to the NDA:

- b(4)**
- a. Data supporting the identity of all impurities exceeding the identification threshold of  $\sim$  % in the drug substance.
  - b. Data supporting the safety of all impurities exceeding the qualification threshold of  $\sim$  % in the drug substance.
  - c. Data supporting the identity of all impurities exceeding the identification threshold of  $\sim$  % in the drug product.
  - d. Data supporting the safety of all impurities exceeding the qualification threshold of  $\sim$  % in the drug product.

### 1.2.3 Other Phase 4 Requests

No Phase-4 requests are recommended.

## 1.3 Summary of Clinical Findings

Based on a single study evaluating safety and tolerability of hydroxocobalamin administration in healthy adults who were not exposed to cyanide, doses of 2.5 g and 5 g were generally well tolerated. The most common adverse reactions included transient chromaturia (red-colored urine), an intense erythema, rash, increased blood pressure, nausea, headache, decreased percentage of lymphocytes, and injection site reactions. Allergic reactions were also observed. The severity and frequency of adverse reactions were generally dose dependent; with the higher doses, 7.5 g and 10 g, being less-well tolerated than the two lower doses. Based on animal studies of efficacy, the 5-g and 10-g human doses of cyanocobalamin should provide increased survival for exposure to lethal doses of cyanide.

### 1.3.1 Brief Overview of Clinical Program

Cyanokit is a lyophilized formulation of hydroxocobalamin (OH-Co) that is proposed for use as an antidote in treating patients with known or suspected cyanide poisoning. It is administered intravenously. It has been studied in adult populations, although it has also been administered to pediatric patients, in France where it was granted marketing authorization in May 1996.

The pivotal trial to demonstrate efficacy was conducted in dogs due to the ethical considerations for human trials. A single human safety, tolerability and pharmacokinetic trial was conducted in which 102 healthy volunteers were exposed to doses of hydroxocobalamin ranging from 2.5 to 10 g. In the same trial, 34 subjects were exposed to doses of placebo, which were vehicle in normal saline similar in volume to the doses of hydroxocobalamin.

In addition to the healthy subject data, the Sponsor was able to provide data from four studies conducted in France, which assessed the use of Cyanokit in the treatment of patients suspected of being exposed to toxic levels of cyanide. None of these studies were controlled, and two of them

were retrospective in design, thereby limiting their usefulness in assessing safety or efficacy. Blood cyanide levels assessed before treatment in three of the studies permitted some assessment of efficacy; adverse events reported were compared to those reported in the safety and tolerability study. In these studies, a total of 245 patients were treated with hydroxocobalamin doses ranging from 1 to 20 g.

### 1.3.2 Efficacy

The only efficacy trial conducted examined the survival rates in dogs which were poisoned with potassium cyanide solutions to the point where they exhibited apnea and then for an additional three minutes. The dogs were mechanically ventilated and treated with either normal saline placebo or a hydroxocobalamin dose of 75 mg/kg or 150 mg/kg. Survival was assessed at Hour 4 following the treatment infusion and at Day 14 following the treatment. The table below summarizes the survival findings.

**Table 1** Survival in cyanide-poisoned dogs (Sponsor's Table 2.5-3; p. 19 of Vol. 2 of Module 2)

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

The 75 and 150 mg/kg doses of hydroxocobalamin correspond to a 5-g and 10-g dose, respectively, in a 70 kg adult.

Two important secondary endpoints were also assessed: blood pressure response and neurologic status following treatment. Dogs treated with hydroxocobalamin exhibited a more rapid recovery of mean arterial blood pressure than placebo-treated dogs. The improvements in blood pressure were observed with the initiation of hydroxocobalamin treatment. These dogs also exhibited a more rapid recovery of minute-volume ventilation compared to placebo-treated animals. Neurologic status included assessment for lethargy, ataxia, dementia and paresis. A lower incidence of these was observed in the hydroxocobalamin-treatment arm than in the placebo-treatment arm. Placebo-treated dogs that did not survive past 4 hours were noted to range from non-responsive to stuporous in level of consciousness following treatment. The animals who survived longer in the placebo-treatment arm and those in the 75 mg/kg OH-Co-treatment arm, which had to be euthanized by Day 4, were noted to have significant neurological deficits; however, dogs which received 150 mg/kg of OH-Co exhibited no neurological abnormalities following treatment. Additionally, it was noted that OH-Co-treated animals had fewer and less severe brain lesions at necropsy than did their placebo-treated counterparts.

The theoretical considerations for dosing, the endpoints selected, the choice of placebo, in addition to the comparison of two OH-Co doses, and the design and conduct of this trial make it adequate and sufficiently well controlled to demonstrate efficacy for hydroxocobalamin as a cyanide antidote.

The French studies assessing hydroxocobalamin treatment of patients with suspected cyanide toxicity provide some support for the findings of the dog study. In particular, the prospective Baud-1 and retrospective Baud-2 and Baud-3 studies included measurements of blood cyanide levels prior to the hydroxocobalamin treatment. These studies suggest that lethal doses of cyanide (those producing blood levels similar to the lethal levels observed in the dog study), when treated with hydroxocobalamin, can be survived. The lack of a comparator, however, limits the interpretation of these findings. These studies also indicated that patients who present in cardiac arrest are substantially less likely to survive than those who do not. The studies also indicated that death generally occurred within 8 days of exposure to cyanide and hydroxocobalamin.

### 1.3.3 Safety

The study of safety and tolerability in healthy volunteers provided the primary source of safety data. Information from the French studies was examined for possible safety concerns associated with the use of hydroxocobalamin in cyanide-poisoned patients; however, the lack of a comparator and the limited amount of data available for review, particularly in the three retrospective studies, severely limited the usefulness of these data. Therefore, the safety of hydroxocobalamin is determined by the results of the study in non-cyanide-exposed volunteers and of animal trials that examined the effects of hydroxocobalamin on blood pressure and evaluated the cardiovascular effects and overall toxicity of cyanocobalamin.

Of the four doses evaluated in the human study, 2.5, 5, 7.5 and 10 g, the two lower doses were generally well tolerated with few adverse events. Those adverse events that occurred at the lower doses tended to occur more intensely and more frequently in the two higher dose groups. There were no deaths or serious adverse events in the study. The most common adverse events included chromaturia and erythema, which were benign and attributable to the color of cobalamins-(III), rash, increased blood pressure, nausea, headache, chest discomfort, injection site reactions, and allergic reactions. Of these, diastolic blood pressure, pustular rash, headache, nausea and chest discomfort were observed in a higher percentage of subjects in the 7.5-g and 10-g-dose groups than in the 2.5-g and 5-g-dose groups.

Elevations in blood pressure, both systolic and diastolic, were observed in all OH-Co-dose groups. The increases began shortly after the OH-Co infusions were initiated and generally resolved without therapy within 4-8 hours after the infusions were completed. Although mean changes were generally modest, some of the levels measured for individual subjects could pose substantial risk to patients who are vulnerable, e.g., patients with aneurysms or bleeding disorders. In patients who are suffering the toxic effects of cyanide, hypotension and shock are not uncommon findings. In these individuals, the pressor effects of hydroxocobalamin could

actually be beneficial. In the French studies, restoration of circulation following administration of hydroxocobalamin was a common observation in patients who presented in shock or cardiac arrest.

Allergic reactions were observed in two subjects in the safety and tolerability study, EML 015722-H101. The presenting symptoms included facial edema and urticaria in one subject who received a 5-g dose of OH-Co; pruritis, erythema and papules on the face, swelling and reddening of the right eye, shivering and dry throat were reported for the second subject who was receiving a 10-g dose of OH-Co that was terminated prematurely due to the symptoms. In the literature, there have been reports of symptoms consistent with allergic reactions including urticaria, angioedema and anaphylactic shock. There were no reported instances of allergic reaction in the French studies, although the design of the studies and the limited data collected make it difficult to assert that no allergic reactions occurred.

Some laboratory abnormalities were observed with OH-Co treatment, but not placebo. These included a decreased lymphocyte percentage with increased neutrophil percentage (but normal cell counts for both), which was more pronounced in the higher dose groups, elevated levels of C-reactive protein, and leukocytosis. The clinical significance of these findings is uncertain. There was also significant interference by cobalamins-(III) in the measurement of several laboratory parameters. These are documented in the review of safety.

There were no clinically relevant changes observed in the ECG recordings of animals or subjects treated with hydroxocobalamin, nor were such changes noted in the arterial blood gas analyses, spirometry and neurological assessments, and physical examinations performed following OH-Co treatments.

Cyanocobalamin is formed when hydroxocobalamin reacts with cyanide. In patients exposed to toxic levels of cyanide and treated with hydroxocobalamin, exposure to substantial levels of cyanocobalamin are likely to ensue. In the dog study designed to assess this situation, there were no reports of significant toxicological findings, even at the highest dose that was feasible to administer, 400 mg/kg. In the published literature, there are reports of cyanocobalamin levels following OH-Co treatment. The reported levels were less than those observed in the dog study suggesting safety and tolerability of cyanocobalamin are not issues for OH-Co-treated humans. In addition, cyanocobalamin has a shorter half-life than hydroxocobalamin in both dogs and humans with normal renal function, thereby reducing exposure, and possibly risk, compared to hydroxocobalamin.

Lastly, review of the safety data available in the French studies, suggested that erythema, rash and chromaturia occur with substantial frequency in cyanide-exposed patients who are treated with hydroxocobalamin. Hypertension, as mentioned above, was rarely observed in this patient population, which was more likely to be suffering from circulatory collapse following their cyanide exposure.

In summary, the safety findings from the animal and human studies indicate that hydroxocobalamin is generally well tolerated at the proposed 5-g starting dose in both cyanide-exposed and cyanide-unexposed patients. Adverse reactions tend to be mild to moderate, and the

more life-threatening reactions, i.e., hypertension and allergic reactions, can be readily assessed and treated if the need arises. The ability to perform clinical laboratory assessments is limited by interference from cobalamins-(III), but the nature of the interference is known. Cyanocobalamin exposure following use of hydroxocobalamin does not appear to impose significant risk on patients compared to the risk of cyanide poisoning.

#### **1.3.4 Dosing Regimen and Administration**

The Sponsor's proposed dosing of 5 g given intravenously over 15 minutes is consistent with the dosing regimen prescribed in the French product label, used in the dog efficacy study, and administered in the safety study conducted on healthy volunteers. It is not consistent with the manner in which the drug was used in the French studies where there was substantial deviation in the duration of the infusions from the labeled recommendations. These deviations included shorter and longer durations of infusions, and likely reflected changes made to compensate for the severity of the patient's condition or response to treatment.

#### **1.3.5 Drug-Drug Interactions**

Drug-drug interactions were not assessed.

#### **1.3.6 Special Populations**

Hydroxocobalamin use was not assessed in any special populations. It is cleared renally, as is cyanocobalamin; however, dosing adjustments for patients with renal insufficiency or renal failure are not recommended as the mechanism of action requires a single molecule of hydroxocobalamin be available to bind a single cyanide group, thereby reducing available cyanide for inducing toxicity.

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## **2 INTRODUCTION AND BACKGROUND**

### **2.1 Product Information**

Cyanokit is the proposed trade name for lyophilized hydroxocobalamin that is distributed in a package containing two 100-mL bottles, each of which contains 2.5 g of drug product, a transfer spike to be used for reconstituting the drug, and intravenous tubing with a vented spike for administration of the drug.

The Sponsor proposes that Cyanokit be approved for the treatment of known or suspected cyanide poisoning in adults. The recommended dose is 5 g administered intravenously over 15 minutes followed by a second 5-g dose, if the first fails to produce a complete response. The second dose may be administered over a period of 15 minutes to 2 hours depending on the patient's cardiovascular, respiratory and neurological status.

### **2.2 Currently Available Treatment for Indications**

Sodium thiosulfate is the only FDA-approved cyanide antidote. The NDA (20-166), held by the U.S. Army, was approved in 1992 but has been discontinued. There is an unapproved product, Cyanide Antidote Kit, which is currently marketed in the United States. The kit includes sodium nitrite and sodium thiosulfate, which are administered intravenously, and amyl nitrite, which is inhaled either by way of a bag-valve-mask/endotracheal-tube device or through saturated cloth material such as a handkerchief or gauze sponge. Sodium nitrite and amyl nitrite are not approved for the treatment of cyanide poisoning; indeed, neither product is approved for use in the United States at the time of this review.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Hydroxocobalamin has been approved in the United States, NDA 085-998, and is marketed for the treatment of Vitamin B<sub>12</sub> deficiency. The approved strength is 1 mg/ml and the maximum dose generally administered is 1 mg intramuscularly. The dose of hydroxocobalamin necessary to treat cyanide poisoning is several thousand times greater. Despite the differences in dosing requirements, it is expected that there should be sufficient active ingredient availability to provide drug product for both indications.

A major safety concern with Vitamin B<sub>12</sub> therapy is allergic reactions. The same has been observed with hydroxocobalamin use in the safety study submitted as part of this NDA.

## 2.4 Important Issues with Pharmacologically Related Products

At present, the only other approved antidote for cyanide poisoning is sodium thiosulfate (NDA 20-166); however, the applicant, the U.S. Army, has discontinued the NDA. Despite the lack of an approved marketed product, sodium thiosulfate in combination with sodium nitrite and amyl nitrite is marketed for treating cyanide poisoning. There have been no data reported in the literature to suggest an efficacy or safety concern with any of the competing products, except for amyl nitrite which has significant abuse potential.

As the military stockpiles antidotes and there has been concern for the safety of troops treated with amyl nitrite in a combat situation, the military has expressed interest in purchasing a product that does not include amyl nitrite. To date, the focus has been on revising the Cyanide Antidote Package or the Cyanide Antidote Kit to contain only sodium thiosulfate and sodium nitrite.

## 2.5 Presubmission Regulatory Activity

The Division identified the following items as issues that needed to be addressed, barring adequate justification for doing otherwise, prior to submission of an NDA for any cyanide antidote:

1. Efficacy must be demonstrated in at least one adequate and well-controlled animal study that evaluated survival as a primary endpoint.
2. Evidence of the suitability of the animal model to reflect human response to both cyanide toxicity and treatment must be provided.
3. Determination of a safety margin between animal and human antidote dosing should be performed.
4. Assessment of the risk for all intermediary and final chemical species related to use of the antidote or its interaction with cyanide must be made with data from either the animal model or human studies.
5. Assessment of the risk for use of the antidote in the absence of cyanide exposure must be made, preferably in a human safety and tolerability study.
6. Pharmacokinetics of the antidote as well as any intermediate and final chemical species, if any, must be characterized.

Several meetings were held with the Sponsor following a request by the Division that they consider seeking approval of Cyanokit in the United States. The focus of these meetings centered on the key items listed above. On March 8, 2001, the Division met with Orphan Medical, Inc. for the first time to discuss the studies that would be required to submit an NDA for Cyanokit (hydroxocobalamin). Orphan Medical had entered into a letter of intent with the Sponsor of Cyanokit in France, Lipla S.A., a subsidiary of Merck. At that meeting and several interactions which followed, the requirements for an NDA submission were refined. The items listed below summarize the requirements. It was anticipated that a cyanide antidote would be

treated as an orphan drug product, would be granted priority review status, and that efficacy would be based on animal studies conducted in accordance with the 21 CFR §314 Subpart I.

Chemistry requirements:

1. An acceptance criteria of  $\leq 0.2\%$  for the level of impurities for both drug substance and drug product would not be acceptable. The ICH identification/specification threshold for degradation products is 0.2%. b(4)
2. An acceptance criteria for bacterial endotoxins, which should comply with the USP monograph, should be provided.
3. A test for free cobalt, or justification for not testing, should be provided.
4. Physical and chemical compatibility studies designed for actual use under realistic conditions will need to be performed.
5. The drug substance is a USP item and should therefore meet USP specifications.

Preclinical requirements:

1. A 28-day intravenous-cyanide poisoning study in dogs using the intended clinical formulation and multiples of the proposed human hydroxocobalamin dose (preferably based on AUC). A rat study could be used instead provided the model can be validated as a human surrogate.
2. Dosing up to the maximum tolerated dose or maximum feasible dose should be evaluated to fully characterize the toxicity profile.
3. Satellite animals should be evaluated for toxicokinetics and recovery profiles.
4. It was recommended that the surviving animals be maintained for (preferably) 30 days to obtain additional safety data. In particular, full histopathological assessment would address some of the concerns for human safety related to the combination of cyanide, hydroxocobalamin and cyanocobalamin exposures. The kidney, heart, lung, spleen, adrenal glands, and brain tissue should be analyzed histopathologically. Brain tissue should also be analyzed with special staining for neuronal as well as glial cell abnormalities.
5. Pharmacokinetic (PK) sampling should be collected through 80-90% of total AUC or least 3-4 times the half-life of the drug.
6. The data obtained in this animal efficacy study will be used to establish the recommended clinical dose.
7. A standard battery of genotoxicity studies, conducted according to ICH guidelines, should be performed in addition to the proposed Ames and rat micronucleus studies, i.e., an *in-vitro* study to evaluate potential chromosomal damage by hydroxocobalamin (e.g., Mouse Lymphoma TK assay)
8. If the study reports from the teratogenicity studies submitted for Cyanokit approval in France are not available for review, a Segment II teratogenicity study should be conducted in rats and rabbits according to GLP guidelines. It could be conducted as a Phase-4 commitment should the L'ippa Sante studies be deemed inadequate to address this issue.
9. Published teratogenicity studies may be submitted provided a complete study report is available, including methodology and animal-data line listings, the appropriate endpoints

are evaluated, blood cyanide levels were monitored, and the study was conducted in accordance with Good Laboratory Practice Guidelines.

10. The plan for safety qualification should be submitted for comment and approval.
11. The levels of substance impurities must be identified in the drug batches used for the proposed 28-day dog study and genetic-toxicology studies.
12. The overall exposure in dogs at the NOAEL dose for the 28-day study should provide a 10-fold safety margin compared to the maximum expected human exposure based on body surface area. The exposure margins should be based upon pharmacokinetic (PK) data (C<sub>max</sub> and AUC values) rather than body weight or body surface area comparison.
13. A rationale for the relevance of the rabbit hypertension mechanism data to the drug product safety profile and how the mechanism studies support the safety of the drug product should be provided.
14. It should be determined whether there is a dose-response relationship for hypertension and skin reaction/rash occur in the dog as they did in the human. The NOAEL for these adverse events should be provided and related to the effective dose as determined from the pivotal dog efficacy study.
15. Photosensitivity should be assessed.
16. Pivotal animal studies conducted as basis for establishing efficacy must be conducted under GLP.
17. The difference in hemodynamic responses to OH-Cb between the species must be evaluated, and the impact that may have for efficacy must be determined.
18. Comparisons of the PK profiles for OH-Cb, cyanide, and CN-Cb in two species should be performed and found to show appreciable similarities with those available for humans.
19. Significant differences between the dog model and humans (either for cyanide, OH-Cb or CN-Cb) for mechanism of action, PK or PD profiles would likely require that another animal model be found.

Clinical requirements:

1. Any difference in hemodynamic responses between the dogs and humans to OH-Cb must be evaluated, and the significance that may have for efficacy must be determined.
2. Comparisons of the PK profiles for OH-Cb, cyanide, and CN-Cb in dogs and humans should be performed and found to show appreciable similarities. Significant differences between the dog model and humans (either for cyanide, OH-Cb or CN-Cb) for mechanism of action, PK or PD profiles would likely require that another animal model be found.
3. Barring justification for doing otherwise, the following endpoints should be studied in a safety and tolerability study in healthy adults:
  - hemodynamics: blood pressure, heart rate, cardiac rhythm (continuous), 12-lead ECGs
  - respiratory: respiratory rate, serum lactate levels, arterial and venous blood gas measurements, pulse oximetry, methemoglobin levels, airway resistance (e.g., auscultation, peak flow, PFTs, as indicated)
  - laboratory: hematology (complete blood counts with platelets and differentials), chemistries (including liver function, renal function, glucose, Ca, phosphate,

- electrolytes), coagulation profiles, levels of atypical hemoglobin complexes, .e.g., methemoglobin
- neurologic: level of consciousness, mental status, motor and sensory evaluation
  - urologic: urinalysis, urine output
  - musculoskeletal/integument: rashes, myalgias, pain at injection sites, irritation of mucosae, tissue injury and/or necrosis
  - post-treatment follow-up for clinical laboratory parameters and adverse events
4. An adequate safety database will minimally consist of 150 subjects exposed to the full antidote product, i.e., all components at their proposed doses, with at least 50 of those exposed to the highest dose.
  5. Before a pediatric study can be considered, the following must be done.
    - Efficacy needs to be firmly established in the animal model.
    - Safety must be demonstrated in adults.
    - Dosing regimens in adults must be supported by safety and efficacy data.
    - Juvenile animal studies may be required depending on findings from adult animal and human data as well as on the ability to determine proper dosing regimens based on the available data.
  6. The need for the administration of a dose of antidote that can neutralize the effect of a lethal dose of cyanide may not be necessary if the route of exposure is such that most victims will die before care providers are available, or are able to establish intravenous access, prepare the antidote for infusion and administer a full dose. Therefore, a decrease in the dose for initial treatment may be warranted and should be considered. (This was reinforced when the human safety and tolerability study was terminated prematurely due to adverse events.)
  7. The safety and tolerability of the exposure to high doses of cyanocobalamin that would result from treatment of cyanide poisoning with hydroxocobalamin should be assessed in both preclinical and clinical studies.
  8. An ISS and ISE will be required for the NDA; to the extent possible, the French data should be incorporated into these sections.
  9. Narratives for each death in the French studies should be included in the NDA. They are required by regulation and should be as detailed as possible. If no information is available for a particular death, that should be documented in the NDA.
  10. A post-marketing surveillance plan must be included with the NDA submission, as this is required for products seeking approval under the animal efficacy rule.
  11. A patient package insert is not required as the product is intended for use in either the pre-hospital or hospital setting.
  12. The fill line should be placed at the 104-ml level of the vial, accounting for the 100 mL of saline plus the 4 mL occupied by the drug substance.
  13. The NDA would be eligible for a rolling review and for fast-track designation.

## **2.6 Other Relevant Background Information**

Cyanokit is commercially available in France and Hong Kong. Rights to the studies of the use of Cyanokit in France were obtained by the Sponsor, and a final study report for each was submitted in support of efficacy and safety of the product when used in the clinical setting.

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### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The CMC review was not available at the time this review was completed; however, in discussions with the review team, it was determined that there were no outstanding issues that would preclude the approval of Cyanokit. The results of an inspection and a study assessing for extractables associated with the tubing included in the drug package were pending. The qualification of impurities was not sufficient to warrant the 27-month expiry that the Sponsor has requested. Instead, the qualifications support a 24-month expiry.

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#### 3.2 Animal Pharmacology/Toxicology

The basis for determining efficacy was the dog study conducted by the Sponsor. A detailed description and analysis can be found in the Pharmacology-Toxicology review, but a brief description of the protocol and a summary of the findings are provided below.

Dogs were evaluated sequentially in this study conducted between March 25 and July 8, 2005. The animals were fasted overnight and anesthetized in the morning with 10 mg/kg ketamine, IV and 0.5 mg/kg diazepam IV. They were intubated and anesthesia was maintained with isoflurane (1.3-2.0%) in air. When a stable Stage-III anesthesia plane was achieved with the animals breathing spontaneously, monitors were applied and catheters were inserted. At least 15 minutes of baseline data were collected, after which, potassium cyanide (KCN) was infused in either the cephalic or saphenous vein at a rate of 0.4 mg/kg/min. When the first apnea occurred (defined as complete cessation of breathing or reduction in tidal volume to less than 4 mL/kg body weight), the KCN infusion was continued for an additional 3 minutes.

At 3 minutes post-apnea, the KCN infusion was stopped, mechanical ventilation was initiated (10 breaths/minute; tidal volume of 15 mL/kg; 100% oxygen), and the study drug (vehicle in normal saline as placebo, 75 mg/kg of hydroxocobalamin or 150 mg/kg of hydroxocobalamin) was infused over 7.5 minutes.

After 15 minutes of mechanical ventilation, the animal was disconnected from the ventilator and allowed to breathe medical grade air through the endotracheal tube. If apnea persisted for 45 seconds, mechanical ventilation was resumed for 15 seconds then stopped to again assess for spontaneous ventilation. This process was repeated up to six times. If all attempts to wean the animal from the ventilator failed, it was euthanized; otherwise, it was allowed to breathe medical grade air for two hours. Those animals who survived the 2-hour weaning period were extubated, had their monitoring discontinued and their catheters removed, and were returned to their cages. They were maintained for up to two weeks and sacrificed on Day 14. Animals that appeared to be in extremis prior to Day 14 were euthanized.

The findings from this study are summarized in the table below, which was taken from the preliminary review of Lawrence Leshin, D.V.M., Ph.D., the primary Pharmacology-Toxicology reviewer.

**Table 2** Survival data for the dog efficacy study (from preliminary review of Lawrence Leshin, D.V.M., Ph.D.)

Dose	Vehicle 0.9% Saline, IV		Hydroxocobalamin 75 mg/kg, IV		Hydroxocobalamin 150 mg/kg, IV	
	M	F	M	F	M	F
Gender						
Body Weight Day 1 (kg)*	10.3 ± 2.1	7.6 ± 0.3	10.0 ± 1.3	8.2 ± 1.0	9.9 ± 1.5	8.1 ± 0.6
Total KCN (mg/kg)*	2.3 ± 0.1	2.3 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	2.3 ± 0.2
Overall by Treatment*	2.3 ± 0.2		2.4 ± 0.2		2.2 ± 0.2	
	KCN doses were within 88% of target dose of 2.5 mg/kg KCN					
Time to Apnea (min)*	2.8 ± 0.3	2.8 ± 0.5	2.9 ± 0.6	2.9 ± 0.4	2.4 ± 0.4	2.8 ± 0.5
Total N	8	9	10	9	9	9
Incidence and Time of Death	<4 hr	6	4		1	
	1					
	2		2			
	3	1			1	
	4	1		1	1	
	14		3			
15			9	6	9	9
% Survival for 14/15 days	0%	33.3%	90%	66.7%	100%	100%

\*Mean ± SD

Other significant findings from the Pharmacology-Toxicology review are described below.

Cyanokit has not been evaluated for carcinogenic potential. No evidence that Cyanokit has potential to cause genetic toxicity was observed in mutagenicity studies, including an *in-vitro* 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.

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## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

Efficacy data was derived primarily from the dog study conducted by the Sponsor.

The Sponsor conducted a single study assessing the safety, tolerability and pharmacokinetics of Cyanokit in healthy adults. This study was the primary source of safety data; additional safety data comes from Sponsor-conducted animal studies designed to address issues raised by the Division during product development when other study results raised safety concerns.

The Sponsor also submitted four French studies that were conducted to gather safety and efficacy data when Cyanokit was used to treat patients with suspected cyanide poisoning.

Lastly, the Sponsor submitted several publications that described the use of Cyanokit in patients.

### 4.2 Tables of Clinical Studies

**Table 3 Clinical Studies**

Study	Purpose	Design	Number of Subjects
EML 015722-H101	safety, tolerability, pharmacokinetics	prospective, placebo-controlled, double-blind, randomized	136
Baud 1	evaluate use on smoke-inhalation victims	prospective, uncontrolled, open-label	69
Baud 2	evaluate use on smoke-inhalation victims	retrospective, uncontrolled, open-label	61
Baud 3	evaluate use on non-smoke-inhalation victims	retrospective, uncontrolled, open-label	14
Fortin	evaluate use on smoke inhalation victims	retrospective, uncontrolled, open-label	101

### 4.3 Review Strategy

The efficacy study in dogs, conducted by the Sponsor, and the healthy human volunteer study assessing safety, tolerability and pharmacokinetics served as the primary sources for determining safety and efficacy of Cyanokit. These studies were the only ones to include control arms and, therefore, permitted comparative analyses. The four uncontrolled, open-label, nonrandomized

human studies conducted in France were evaluated for safety signals and data suggesting efficacy for Cyanokit use in humans exposed to cyanide. The lack of comparators in the French studies limited the usefulness of the data. Literature was also reviewed for data suggestive of a safety concern with Cyanokit. Most of the literature was anecdotal reporting of use in individual or small numbers of patients.

The evaluation of the animal studies by the Pharmacology-Toxicology review team was relied upon for the determination of efficacy and an assessment of how safety concerns noted in the animal studies may apply to humans. The statistics team also evaluated the data and the Sponsor's planned analyses for the dog study to confirm the results.

#### **4.4 Data Quality and Integrity**

As the regulatory action to be taken for Cyanokit relies heavily on one animal and one human subject study, the latter conducted abroad, the Division of Scientific Investigations was asked to inspect the clinical site in Germany, the analytical sites in Germany and France, and the animal study site in the United States. These were not "for cause" inspections. The findings of these investigations were still pending at the time of this review.

#### **4.5 Compliance with Good Clinical Practices**

The dog survival study and the safety, tolerability and pharmacokinetics study in healthy volunteers were conducted according to Good Laboratory Practice Regulations and Good Clinical Practice Guidelines, respectively. The human protocol was reviewed and approved by the Independent Ethics Committee at the Chambers of Physicians in Berlin. The principles of the Declaration of Helsinki were, according to the Sponsor, also observed.

At the time of this review, results of inspections by the Office of Scientific Investigations for both of these study sites were pending. These inspections were requested because these studies represented the primary sources of efficacy and safety data for this NDA and formed the basis of the benefit-risk analysis for the regulatory action to be taken.

#### **4.6 Financial Disclosures**

The Sponsor executed and submitted Form OMB No. 0910-0396 certifying that EMD Pharmaceuticals, Incorporated, did not enter into any financial arrangements with the clinical investigators that could affect the outcome of the study. The Sponsor reported that financial disclosure forms were collected from all but one of the Investigators. That Investigator, Gunnar

Clinical Review  
Arthur Simone, M.D., Ph.D.  
NDA 22-041  
Cyanokit (hydroxocobalamin)

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Muller, resigned before the absence of his form was noted. The forms were not submitted with the NDA for Agency review.

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## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

Study EML 015722-H101 was conducted, in part, to assess the pharmacokinetics of hydroxocobalamin in healthy adult volunteers. The protocol is described in the Appendix; the pharmacokinetic conclusions drawn by the Sponsor are listed below.

1. The mean  $t_{max}$  of free cobalamins-(III) occurred at the end of the infusions for all dose groups. The mean  $t_{max}$  of total cobalamins-(III) occurred slightly later than  $t_{max}$  of free cobalamins-(III) for all dose groups.
2. Total cobalamins-(III)  $C_{max}$  and  $AUC_{0-t}$  increased almost proportionally over the dose range studied.
3. The ratio of free to total cobalamins-(III) for both  $AUC_{0-t}$  and  $AUC_{0-\infty}$  was approximately 5% in all dose groups.
4. The percentage of total cobalamins-(III) excreted in urine from time zero to infinity ( $Ae_{0-\infty}$ ) ranged from 58% to 74 %, suggesting that hydroxocobalamin is eliminated largely via the renal route of excretion.
5. The mean apparent terminal half-life of free and total cobalamins-(III) ranged from approximately 26-33 hours and appeared to be independent of dose.
6. Total systemic clearance of both the free and the total cobalamins-(III), 208-220 mL/m, did not change over the dose range studied. Clearance of the free fraction exceeded the glomerular filtration rate by two-fold, which was attributed to protein binding.
7. Renal clearance appeared to decrease at the 10-g dose level without a change in total clearance.
8. Renal and total clearance of total cobalamins-(III) were slightly lower in female than male subjects.

### 5.2 Pharmacodynamics

Pharmacodynamic effects of hydroxocobalamin related to cyanide poisoning were not assessed in clinical or preclinical trials. The temporal relationship between administration of hydroxocobalamin and the commonly observed side effects were assessed in Study EML 015722-H101 and are described in Section 7 of this review.

### 5.3 Exposure-Response Relationships

Exposure-response relationships were not evaluated in any human study.

Because the time necessary to confirm cyanide poisoning is substantially longer than the time for cyanide to exert its lethal effects for most types of exposures, treatment with a dose sufficiently large to prevent death was considered an appropriate starting dose. This dose was determined by calculating the amount of hydroxocobalamin needed to bind a lethal dose of cyanide in an average sized adult. The same dosing determination was used for the efficacy study conducted in dogs.

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## **6 INTEGRATED REVIEW OF EFFICACY**

### **6.1 Indication**

The Sponsor seeks an indication for the treatment of known or suspected cyanide poisoning.

#### **6.1.1 Methods**

The determination of efficacy was based on the findings of the dog study described in Section 3.2 above and reviewed in detail in the Pharmacology-Toxicology review.

#### **6.1.2 General Discussion of Endpoints**

The primary endpoint, survival, was a requirement by the Division, as was assessment for major morbidity among survivors. Based on the potential for rapid death or catastrophic morbidity secondary to tissue hypoxia following cyanide exposure, these two endpoints were considered pivotal for assessing efficacy and performing a benefit-risk analysis.

#### **6.1.3 Study Design**

The design of the dog study is briefly described in Section 3.2 above and reviewed in detail in the Pharmacology-Toxicology reviews. The development of the protocol was based on the interactions between the Sponsor and the Agency.

Overall, the study was adequate and appropriately designed to assess survival with treatment following life-threatening exposure to cyanide. The use of a placebo and two doses of hydroxocobalamin permitted an assessment of dose response in addition to simple determination of efficacy. A shortcoming of the study was the inability to assure treatment blinding. The change in color of the animals' skin that occurred with hydroxocobalamin treatment could not be avoided and could not be artificially induced for the placebo-treatment group. The concern of the lack of blinding in a survival study stems from the protocol-specified euthanization of animals determined to be in agonal states. The possibility that animals with red-colored skin were permitted a longer opportunity to recover than those that had normal-colored skin which were euthanized per protocol, cannot be completely eliminated. The inclusion of two hydroxocobalamin-dose groups may have eliminated this bias provided the Investigator who made the decision was blinded to the dose any particular animal received.

### 6.1.4 Efficacy Findings

The table below summarizes the findings of the dog efficacy trial and indicates that hydroxocobalamin confers a survival benefit exceeding that of placebo. In addition, the study showed survival was also dose dependent.

**Table 4 Dog Survival (from the primary Pharmacology-Toxicology review)**

Dose		Vehicle 0.9% Saline, IV		Hydroxocobalamin 75 mg/kg, IV		Hydroxocobalamin 150 mg/kg, IV	
Gender		M	F	M	F	M	F
Body Weight Day 1 (kg)		10.3 ± 2.1	7.6 ± 0.3	10.0 ± 1.3	8.2 ± 1.0	9.9 ± 1.5	8.1 ± 0.6
Total KCN (mg/kg)		2.3 ± 0.1	2.3 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	2.3 ± 0.2
Overall by Treatment		2.3 ± 0.2		2.4 ± 0.2		2.2 ± 0.2	
KCN doses were within 88% of target dose of 2.5 mg/kg KCN							
Time to Apnea (min)		2.8 ± 0.3	2.8 ± 0.5	2.9 ± 0.6	2.9 ± 0.4	2.4 ± 0.4	2.8 ± 0.5
<b>Total N</b>		<b>8</b>	<b>9</b>	<b>10</b>	<b>9</b>	<b>9</b>	<b>9</b>
Incidence and Time of Death	<4 hr	6	4		1		
	1						
	2		2				
	3	1			1		
	4	1		1	1		
	14		3				
	15			9	6	9	9
<b>% Survival for 14/15 days</b>		<b>0%</b>	<b>33.3%</b>	<b>90%</b>	<b>66.7%</b>	<b>100%</b>	<b>100%</b>

Mean ± SD

In addition to the dog study, there was also data from the Baud Studies of hydroxocobalamin use in humans that included pretreatment assessments of blood cyanide levels. Although the studies did not include a comparator arm, the blood levels of cyanide for some of the patients were in the range associated with lethal outcomes in humans, as reported in the literature, as well as with the blood cyanide levels observed in the dog study of efficacy (115 µmol/L). The table below summarizes the findings and suggests a possible survival benefit with hydroxocobalamin, particularly in patients who were not in cardiac arrest when found by rescuers.

**Table 5 Summary of findings for Baud Studies.**

Parameter	In cardiac arrest <sup>1</sup>			Not in cardiac arrest <sup>2</sup>			Group Summary <sup>3</sup>		
	Blood cyanide level (µmol/L)	Survival	OH-Co Dose (g)	Blood cyanide level (µmol/L)	Survival	OH-Co Dose (g)	Blood cyanide level (µmol/L)	Survival	OH-Co Dose (g)
Number of Patients	11	3/11 (27%)	11	22	17/22 (77%)		33	20/33 (61%)	33
Mean	166		8.8	170		7.0	168		7.6
S.D.	44		3.0	48		3.7	46		3.5
range	103-239		5-15	100-260		5-20	100-260		4-20

- <sup>1</sup> All but one patient, whose value was not recorded, had Glasgow Coma Scores of 3. The mean carbon monoxide level which was measured in 8 patients was 3.8 mmol/L; the range was 2.1-5.
- <sup>2</sup> The mean Glasgow Coma Score was 10.5; the range was 3-15. The mean carbon monoxide level which was measured in 13 patients was 3.8 mmol/L; the range was 1.1-10.
- <sup>3</sup> The mean Glasgow Coma Score was 8.2; the range was 3-15. The mean carbon monoxide level which was measured in 21 patients was 3.8 mmol/L; the range was 1.1-10.

### **6.1.5 Clinical Microbiology**

Not applicable for this drug product.

### **6.1.6 Efficacy Conclusions**

The data from the dog survival study demonstrated that hydroxocobalamin can prolong survival, restore circulation and improve neurological status in animals exposed to lethal levels of cyanide. The data also indicated that the large doses of cyanocobalamin which resulted from the treatment are generally well tolerated.

In discussions with the Sponsor, it was determined that a single animal efficacy study, if properly designed and executed, could be sufficient for establishing efficacy of an antidote. This study appears to have met those requirements.

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## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The data sources for the safety review included the study report for the healthy human volunteer study, which assessed the pharmacokinetics, safety and tolerability of hydroxocobalamin in non-cyanide exposed individuals; the study reports for the French experience with Cyanokit use, which includes the Baud-1, Baud-2, Fortin and Baud-3 studies; and the literature reports documenting the use of hydroxocobalamin in patients who were not part of the above studies.

As the time required to confirm a diagnosis of cyanide poisoning is substantially longer than the time required for cyanide to exert its lethal effects when it is inhaled or ingested, treatment consists of supportive therapy along with antidote administration based on a presumptive diagnosis. Therefore, safety has been reviewed from two perspectives: first, the use of hydroxocobalamin in individuals who were either not exposed to cyanide or were exposed to non-toxic doses of cyanide, and, second, the use of hydroxocobalamin in individuals who were exposed to toxic doses of cyanide. A full assessment of safety cannot readily be made for patients in either of these two categories for reasons discussed below.

The available safety data for non-cyanide exposed individuals comes from the healthy volunteer study. This data was useful for evaluating the effects of hydroxocobalamin in individuals not suffering from the effects of cyanide toxicity and had the benefit of inclusion of a placebo-treatment arm. The limitation of this study was that it did not permit the evaluation of the effects of hydroxocobalamin when administered to poisoning victims suffering the effects of non-cyanide toxins or when administered to non-cyanide-toxic victims suffering other injuries such as burns, fractures or smoke-inhalation pulmonary injury. There is some data from the Baud studies which address this issue, but the small numbers of patients and the lack of comparators make a benefit-risk analysis difficult.

The safety data from the studies evaluating patients who were exposed to toxic levels of cyanide are limited in their interpretation by the lack of a comparator arm and the concomitant exposure in all but a few cases to other toxins. The exposure to additional toxins, most notably carbon monoxide for smoke-inhalation victims, makes it difficult to definitively identify adverse reactions related to the use of hydroxocobalamin in these patients. The Baud-3 study included a relatively small number of patients whose exposure was limited to cyanide alone, mostly those attempting suicide. However, the usefulness of this data is limited by both the small population size and the lack of a comparator. While one of these studies was prospective, the circumstances under which it was conducted, i.e., the scene of a fire, hospital emergency rooms and ICUs, made data collection challenging at best. The Sponsor made an effort to review the available records and retrospectively, at the Division's request, supplement the available data with additional vital sign, laboratory assessment and physical exam findings where possible.

Lastly, the literature reports provide primarily anecdotal information from a small number of patients which was of limited use in the safety assessment.

The key safety findings from the healthy volunteer study included the following:

- The recommended 5-g dose of hydroxocobalamin as the initial treatment was generally well tolerated.
- The recommended upper limit of hydroxocobalamin dosing, 10 g, was associated with the same types of adverse reactions observed in the 5-g dose group; however, the frequency and intensity of the reactions were substantially increased.
- There were no deaths or serious adverse events reported for the study.
- Adverse reactions posing the greatest risk to safety were hypertension, particularly diastolic hypertension, and allergic reactions.
- Non-life-threatening reactions included intense erythema, chromaturia, rashes, nausea, headache and injection site reactions.
- Adverse reactions generally occurred shortly after the hydroxocobalamin infusion was initiated, improved over minutes to hours following termination of the infusion, and responded readily to symptomatic therapeutic intervention.
- The more life-threatening reactions, hypertension and allergic reactions, are readily detected with simple monitoring and treated with relative ease if they are detected early.

The key safety findings from the four cyanide-poisoned-patient studies included the following:

- The intense erythema and chromaturia observed in the safety and tolerability study were commonly observed in these patients as well.
- Hypertension was a rare occurrence in these patients following hydroxocobalamin treatment. Many cyanide-exposed victims presented in cardiac arrest or shock. These patients often experienced restoration of cardiovascular status concomitant with hydroxocobalamin treatment.
- Signs and symptoms suggestive of allergic reactions were reported for some patients; there were no reports of anaphylactic reactions temporally related to hydroxocobalamin administration.
- There were no signals suggestive of a safety concern that were not observed in the safety and tolerability study.

The review of the literature indicated the same findings noted in the Baud and Fortin studies. Similarly, there was no indication of a safety concern that was not observed in the safety and tolerability study.

### 7.1.1 Deaths

There were no deaths in the healthy volunteer study. There were a total of 89 deaths associated with the four studies involving the treatment of cyanide-poisoning victims. A table providing summary information for each death and narrative descriptions of the clinical course for each of these patients can be found in **Appendix 10.4** of this review. All of the patients who died in

these studies were exposed to toxic substances prior to the initiation of therapeutic interventions and treatment with Cyanokit. These exposures and the patients' conditions at the time of rescue were sufficiently severe that mortality was not an unexpected outcome. The lack of a comparator in each of these studies makes it impossible to determine whether Cyanokit may have increased the mortality rate or hastened the demise for patients in the situations studied.

Of the 84 patients for whom dosing information was available, 54 (64%) received a 5-g dose of Cyanokit; 13 (15%) received a 10-g dose; and 7 (8%) received doses greater than 10 g. The doses ranged from 1 to 20 g. Five of the 10 doses less than 5 g were administered to pediatric patients ages 2-5 years old; one dose was administered to a 94 year old woman.

Approximately one third of the patients died on the day of treatment; the mortality rate declined exponentially after that. Just over half the deaths occurred by Day 2; a single patient survived to Day 30.

The table below provides summary demographic characteristics for the patients who died and compares them to those who survived.

**Table 6** Demographics of patients who died

Parameter	Total Study Population	Subjects Who Died (% of Total Study Population value)
<b>Gender</b>		
Male	128	38 (30)
Female	117	51 (40)
<b>Age (years)</b>		
< 18	9	6 (67)
≥ 18 and < 65	179	59 (33)
≥ 65	52	25 (48)
<b>Cardiac arrest prior to treatment</b>		
Yes	72	65 (90)
No	173	24 (14)
<b>Glasgow Coma Score</b>		
= 3	83	63 (76)
<b>Blood cyanide levels (µmol/L)</b>		
< 40	37	9 (24)
≥ 40 and < 100	28	8 (29)
≥ 100	33	13 (39)

Patients who were in cardiac arrest at the time rescuers arrived [63/89 (71%)] or who went into cardiac arrest prior to treatment with Cyanokit [2/89 (2%)] composed the majority (73%) of victims who died. Female patients comprised the majority (60%) of patients who were in cardiac arrest prior to the administration of Cyanokit. The ratios by gender are identical for female to

male deaths overall and female to male patients in cardiac arrest prior to treatment, suggesting this is could account for the difference in mortality rates seen by gender above.

Glasgow Coma Score (GCS) was not as closely associated with death as pretreatment cardiac arrest, but there was a fairly strong trend in that direction. Sixty-three (71%) of the patients who died had a Glasgow Coma Score of 3 when rescuers arrived; ten patients (11%) had scores of 13-15.

The data from the studies are supportive of a 100 µmol/L cutoff for the lethal blood level of cyanide as there is a substantial increase in mortality for patients with levels above this value. The relatively high mortality rates observed in patients with blood levels < 100 µmol/L suggest that other factors may be contributing to mortality; in particular, prolonged hypoxia may be causing irreparable damage to the brain and heart.

The table below summarizes the causes of death for the patients in the individual studies. For this table, similar causes of death were grouped so that listings such as “refractory shock,” “hemodynamic collapse,” and “cardiovascular failure” are all listed under “Shock.”

**Table 7 Summary of causes of death for all studies**

Cause of Death	Study				
	Baud 1	Baud 2	Baud 3	Fortin	Overall
Cardiac Arrest <sup>1</sup>	3	5		21	29
Shock	3	8	2	3	16
Brain Death	3	5	2	4	14
Multiple Organ Failure		2		8	10
Septic Shock	5	2		1	8
Therapy Discontinued	3			2	5
Unknown		1		3	4
Pneumonia	1				1
Electromechanical Dissociation	1				1
Hyperkalemia		1			1

<sup>1</sup> Subjects who were found in cardiac arrest and died at the scene were assumed to have died of cardiac arrest unless there was information indicating otherwise.

### 7.1.2 Other Serious Adverse Events

No serious adverse events were reported in Study EML 015722-H101 conducted by the Sponsor, and no serious adverse events were reported for any of the four French clinical experience studies: Baud 1, 2 and 3 and Fortin.

### **7.1.3 Dropouts and Other Significant Adverse Events**

Subject 4018 in Study EML 015722 – H101 was the only subject to discontinue treatment; the discontinuation was in association with an adverse event. All other subjects in this safety and tolerability study of healthy volunteers completed their treatments.

#### **7.1.3.1 Overall profile of dropouts**

Subject 4018 was a 26 year old Caucasian female who was scheduled to receive a 10-g dose of hydroxocobalamin in the Phase-2 study examining the safety and tolerability of hydroxocobalamin administered to healthy volunteers. The subject reported pruritis, especially of the face and neck, five minutes after the infusion of study drug was begun. Over the next few minutes, this was followed by additional allergic symptoms including erythema and papular rash on the face and swelling and reddening of the right eye. The patient also reported a dry throat and shivering starting at the same time. Based on the severity of the symptoms and the rapidity with which they developed, the Investigator terminated the infusion after 12 minutes. At that point in time, a total of 156 mL of study drug, 3.9 g of hydroxocobalamin, had been infused.

The patient was treated a 4-mg dose of dimetindenmaleate (an antihistamine), i.v., two minutes after the study-drug infusion was discontinued. Her condition improved and fully resolved approximately an hour after her symptoms began.

#### **7.1.3.2 Adverse events associated with dropouts**

No other adverse events were associated with the single dropout.

#### **7.1.3.3 Other significant adverse events**

In Study EML 015722 – H101, the following adverse events did not meet the definition of serious and did not lead to death or modification of therapy, but they may potentially affect how the drug is administered or require intervention.

1. Hypertension
2. Rash
3. Nausea
4. Headache
5. Injection site reactions

Adverse events (AEs) for this study are described below in dosage-based groups.

#### **2.5-g Dose**

No subject receiving placebo had an adverse event.

There were 23 AEs reported in the nine subjects who received the active treatment. All subjects had red colored urine, chromaturia, which was described as “intense” rather than “severe” as it was not associated with any discomfort or inability to perform normal daily activities. All other AEs were described as mild or moderate. Among those which the Investigators attributed to study drug were two occurrences each of vomiting and hypertension, and one occurrence each of nausea, headache, and decreased white blood cell count (i.e., a decrease in percent of lymphocytes to < 10%; the absolute number was within normal limits). Not considered by the Investigators as related to study drug were three incidents of common cold, and one incident each of tiredness, palpitations, headache and increased creatine kinase (CK). The increase in CK occurred two weeks following treatment and appeared to be associated with vigorous physical activities by the subject. The peak CK value was reported as 1632 U/L (normal range: 0-142 U/L); it returned to normal, 87 U/L, about 10 days later.

Only two subjects received treatment for their AEs:

- Subject 1001 received one dose of 400 mg of ibuprofen for a headache which began 5 minutes after the start of the study drug infusion and lasted approximately 10 hours.
- Subject 1004 had a “common cold” starting 10 days after the study drug infusion. It was treated with dextromethorphan, paracetamol and phenylpropanolamine one day after the onset of symptoms, and it resolved four days later.

#### 5-g Dose

In this treatment group, nine of the 22 subjects receiving placebo reported a total of 11 AEs. These were rated as mild to moderate and included three incidents of nasopharyngitis, two incidents each of headache and decreased hemoglobin levels, and one incident each for nausea, peripheral edema, sensation of pressure, increased C-reactive protein (CRP).

There were 234 AEs recorded for the 66 subjects who received active treatment. All subjects had “intense” chromaturia. Erythema (“skin redness”) or generalized erythema was reported in 62 (94%) of the subjects and was rated as intense (similar to the chromaturia) or moderate. Excluding the color changes in the urine and skin, the remaining AEs occurred in 49 (74%) of the subjects. Pustular rash was reported in 11 subjects (17%); headache was reported for seven subjects (11%), and six subjects (10%) had increased blood pressure, increased diastolic blood pressure, and decreased lymphocyte count. Injection site erythema was reported twice. The remaining AEs were considered possibly or not likely related to the study drug and included ventricular extrasystoles, gastroenteritis, nasopharyngitis, increased CK and CRP, decreased hemoglobin, dizziness, headache, dysuria, pollakisuria (urinary frequency), dysmenorrhea, dry throat, pharyngolaryngeal pain and thrombophlebitis.

Ten subjects received treatment for their adverse events; among these were eight subjects who had received hydroxocobalamin treatment:

- Subject 2001 switched medications for treatment of an ongoing climacteric disorder on the advice of her gynecologist without consulting the Investigator. She received a 5-g dose of OH-Co as her study treatment.

- Subject 2010 experienced a headache starting 36 hours after her study-drug infusion. She was given 500 mg of paracetamol after 1.5 hours; the headache resolved after another 1.25 hours. The treatment was in violation of the protocol.
- Subject 2011 reported restlessness, change of feeling between warm and cold, sensation of dryness in the throat, erythema, edema in the face and mouth and dyspnea, all starting close to the initiation of the treatment. The subject was treated with 4 mg of dimetindenmaleate (a histamine antagonist) i.v. and 40 mg of dexamethasone i.v. An hour and 10 minutes later, the AEs had resolved without sequelae.
- Subject 2065 received 200 mg of ibuprofen for menstrual pain 27 hours after the start of study-drug infusion.
- Subject 2068 had increased diastolic pressure first measured as 114 mmHg at 5 minutes following start of infusion. The pressure increased to 133 mmHg at 22 minutes and then decreased to 107 mmHg at about 30 minutes after the start of the infusion. It was treated with 10 mg of urapidil (an alpha-adrenergic blocking agent) p.o. given at 26 minutes after onset, resulting in the decline to 107 mmHg noted at 30 minutes. The diastolic blood pressure remained below 110 mmHg for the remainder of the day; the last measurement, 98 mmHg, was taken at about 9:45 p.m.
- Subject 2071 had a common cold about 18 days after the infusion. It was treated with 500 mg acetylsalicylic acid twice on the first day symptoms were experienced. The cold resolved 3 days later.
- Subject 2086 also suffered from a common cold starting about 19 days after the infusion. It was treated with 500 mg of paracetamol and 300 mg of roxithromycin daily for 1 week.
- Subject 2087 had a headache at 6 days following the infusion and was treated with 500 mg acetylsalicylic acid. The headache lasted 22 hours.

#### 7.5-g Dose

In the placebo group for this treatment, two of the three subjects experienced five AEs described as mild to moderate in severity and not considered, by the Investigator, as related to the treatment. These events included cough, dizziness, headache, increased bilirubin and decreased blood phosphorus.

In the nine subjects who received active treatment, there were 60 AEs. All subjects experienced chromaturia and erythema; headache occurred six times in five subjects; increased diastolic pressure was reported at five different assessments in five subjects; and pustular rash was observed four times in four subjects. Decreased lymphocyte count and infusion site erythema were noted three times; pruritus and throat tightness were reported three times each in two subjects. The following events were listed as single occurrences: vomiting, increased CK, dyspepsia, dyspnea, dizziness, dysphagia, increased CRP, hyperhidrosis and discomfort. Two reports of nasopharyngitis ("common cold"), one case of headache and one case of increased CK were also reported but were considered unlikely related to treatment by the Investigator.

No subjects in either treatment group required treatment for their adverse events.

10-g Dose

Four of the six subjects who received placebo treatment experienced seven AEs, none of which were considered by the Investigator to be drug related. These AEs included decreased blood pressure and cannula site reaction (both occurred immediately before study drug administration), back pain, headache, thrombophlebitis, peripheral coldness and paresthesia. All were described as mild to moderate in severity.

The 18 subjects who received active treatment reported chromaturia and erythema. Erythema at the infusion site was observed eight times in seven subjects; headache was reported seven times for six subjects; and increased diastolic blood pressure was recorded seven times in five subjects. Four subjects reported dysphagia while other additional gastrointestinal disorders were recorded for five subjects. These included two episodes of abdominal discomfort, two episodes of nausea, and one episode each of "bowel movement," diarrhea, gastric disorder, hematochezia, abnormal feces, stomach discomfort. Three subjects had a combination of papular rash, pustular rash, pruritus and decreased lymphocyte count. Two subjects reported eye irritation, redness and swelling. Two subjects had exanthema, and four subjects reported chest discomfort (two episodes), throat tightness (two episodes) and dry throat.

Two subjects were observed to have renal pain, dysuria, and cystitis; one occurred two days following the OH-Co infusion, the other began 17 days following treatment with study drug. The first resolved over the course of 24 hours without treatment; the second required treatment (see below) and resolved after 11 days.

The following AEs occurred once each and were considered by the Investigator to be either not related or unlikely related to study treatment: periorbital hematoma (related to a fight), increased CK, cystitis, increase in triglycerides and herpes simplex.

The following subjects received OH-Co infusions and required treatment for their adverse events.

- Subject 4008 was treated for cystitis which began 17 days after study-drug infusion. Treatment consisted of 250 mg of ciprofloxacin b.i.d. for 6 days. The cystitis resolved after 11 days.
- Subject 4013 reported a moderate headache about 10 hours after study treatment and was given 400 mg of ibuprofen the next day. The headache lasted a total of 27 hours.
- Subject 4015 also reported a headache about 10 hours following study-drug infusion. Her headache lasted seven days, but the only treatment given was ibuprofen 400 mg administered in the morning on the second and third day of the headache and 200 mg administered in the afternoon on the second day.
- Subject 4018 was assumed to have had an allergic reaction starting at 8 to 10 minutes after initiation of the OH-Co infusion. The infusion was stopped and 4 mg of dimetindenmaleate i.v. was administered six minutes after the onset of symptoms, which included itching skin and erythema of the face. The symptoms were reported to resolve quickly following treatment.

- Subject 4020 reported a severe headache starting five hours after the study-drug infusion was initiated. Ten hours after the onset, the subject took 500 mg of acetylsalicylic acid. The headache resolved after 34 hours.

#### **7.1.4 Other Search Strategies**

The limited amount of data available and the lack of comparators in the French studies precluded obtaining meaningful results from additional search strategies.

#### **7.1.5 Common Adverse Events**

##### **7.1.5.1 Eliciting adverse events data in the development program**

In Study EML 015722-H101, the Sponsor prespecified criteria for reporting laboratory data and patient monitoring results as adverse events and also provided criteria for assessing their severity or clinical relevance, as per the Division's request. Frequent protocol-mandated assessments permitted ample opportunity for capturing subject-reported adverse events and detecting changes in subjects' clinical status.

The Sponsor also attempted, where possible, to predefine adverse event criteria for the data collected in the French studies; however the retrospective analyses of these studies often precluded further evaluation, e.g., repeat or additional testing, and patient follow-up assessments.

##### **7.1.5.2 Appropriateness of adverse event categorization and preferred terms**

MedDRA was used to report adverse events. The categorization of events using preferred terms appeared to be appropriate based on review of the adverse event tables from each of the submitted human studies.

##### **7.1.5.3 Incidence of common adverse events**

The healthy volunteer study provided the only controlled basis for assessing adverse drug reactions. The safety data from the French studies was also evaluated for adverse drug reactions by assessing for reactions that exhibited dose dependence. This effort was thwarted in part by the lack of uniform collection of adverse-event data in the different studies and the limited patient information available to the Sponsor for assessing adverse events in the retrospective trials. In addition, the usefulness of the evaluation is limited because the use of higher doses of Cyanokit was generally associated with patients who presented in a more toxic state and, therefore, were more likely to experience adverse events secondary to their underlying condition and more likely to require additional therapeutic interventions each with its own adverse-event profile.

#### 7.1.5.4 Common adverse event tables

The table below lists the adverse events for the four French studies and the healthy volunteer study; it is based on the one submitted by the Sponsor in an e-mail dated October 13, 2006, which was generated at the request of the Division. As the French studies were uncontrolled and had suboptimal means of assessing for adverse events, the data for all four trials were combined without regard to dose administered or the type and level of cyanide exposure involved. Data from the healthy volunteer study is separated by treatment arms. A frequency cutoff of 5% was used in developing this table. This cutoff retained the important adverse events observed in the healthy volunteer study and allows comparison to the events observed in the treatment of poisoned patients. Rare but concerning adverse events noted in the French studies are described below in Section 7.1.6.

A table provided by the Sponsor listing all adverse events with separation by OH-Co dose for the French studies and treatment arm for the healthy volunteer study is included in the appendix.

**Table 8** Listing of adverse events occurring in more than 5% of subjects for all studies

Adverse Events	Combined French Studies	Healthy Volunteer Study				
	All OH-Co Doses	Placebo	2.5 g	5 g	7.5 g	10 g
	N=245 n (%)	N=34 n (%)	N=9 n (%)	N=66 n (%)	N=9 n (%)	N=18 n (%)
<b>Blood And Lymphatic System Disorders</b>						
total	11 (4)	0	0	0	0	0
<b>Cardiac Disorders</b>						
total	34 (14)	0	1 (11)	1 (2)	0	0
cardiac arrest	12 (5)					
palpitations			1 (11)			
<b>Eye Disorders</b>						
total	25 (10)					
eye irritation	2 (<1)					1 (6)
eye swelling						1 (6)
eyelid edema	1 (<1)					1 (6)
<b>Gastrointestinal Disorders</b>						
total	19 (8)	1 (3)	1 (11)	7 (11)	4 (44)	8 (44)
abdominal discomfort				2 (3)	2 (22)	2 (11)
abnormal feces						1 (6)
diarrhea	3 (1)					1 (6)
dyspepsia					1 (11)	
dysphagia	1 (<1)				1 (11)	4 (22)
frequent bowel movements						1 (6)
gastric disorder						1 (6)
hematochezia						1 (6)
nausea	2 (<1)	1 (3)	1 (11)	4 (6)	2 (22)	2 (11)
stomach discomfort						1 (6)
vomiting	7 (3)		1 (11)	2 (3)	1 (11)	

Adverse Events	Combined French Studies	Healthy Volunteer Study				
	All OH-Co Doses	Placebo	2.5 g	5 g	7.5 g	10 g
	N=245 n (%)	N=34 n (%)	N=9 n (%)	N=66 n (%)	N=9 n (%)	N=18 n (%)
<b>General Disorders And Administration Site Conditions</b>						
total	24 (10)	2 (6)	1 (11)	9 (14)	3 (33)	11 (61)
chest discomfort				3 (5)		2 (11)
discomfort				1 (2)	1 (11)	
fatigue			1 (11)			1 (6)
induration						1 (6)
infusion site erythema				2 (3)	3 (33)	7 (39)
infusion site induration						1 (6)
infusion site pain						1 (6)
infusion site swelling						1 (6)
edema peripheral	1 (<1)	1 (3)				2 (11)
rigors						1 (6)
<b>Infections And Infestations</b>						
total	59 (24)	3 (9)	2 (22)	16 (24)	6(67)	4 (22)
cystitis						1 (6)
herpes simplex						1 (6)
nasopharyngitis		3 (9)	2 (22)	6 (9)	2 (22)	
pneumonia bacterial	15 (6)					
rash pustular				11 (17)	4 (44)	3 (17)
<b>Injury, Poisoning And Procedural Complications</b>						
total	1 (<1)	0	0	0	0	1 (6)
periorbital hematoma						1 (6)
<b>Investigations</b>						
total	11 (4)	5(15)	3 (33)	23 (35)	8 (89)	10 (56)
blood creatine phosphokinase increased	1 (<1)		1 (11)	1 (2)	1 (11)	1 (6)
blood pressure diastolic increased				6 (9)	5 (56)	5 (28)
blood pressure increased	2 (<1)		2 (22)	6 (9)		
blood triglycerides increased						1 (6)
c-reactive protein increased				4 (6)	1 (11)	1 (6)
hemoglobin decreased		2 (6)		2 (3)		
lymphocyte count decreased				6 (9)	3 (33)	3 (17)
white blood cell count decreased			1 (11)			
<b>Metabolism And Nutrition Disorders</b>						
total	47 (19)	0	0	0	0	0
hypercreatininemia	15 (6)					
hyperglycemia	26 (11)					
<b>Musculoskeletal And Connective Tissue Disorders</b>						
total	5 (2)	1 (3)	0	2 (3)	0	1 (6)
muscle cramp						1 (6)
<b>Nervous System Disorders</b>						
total	27 (11)	3(9)	2(22)	7(11)	5(56)	7(39)
dizziness		1(3)		2(3)	1(11)	1(6)
headache	2 (<1)	3(9)	2(22)	6(9)	5(56)	6(33)

Adverse Events	Combined French Studies	Healthy Volunteer Study				
	All OH-Co Doses	Placebo	2.5 g	5 g	7.5 g	10 g
	N=245	N=34	N=9	N=66	N=9	N=18
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
memory impairment						1(6)
<b>Psychiatric Disorders</b>						
total	12 (5)	0	0	2 (3)	0	0
<b>Renal And Urinary Disorders</b>						
total	43 (18)	0	9 (100)	66 (100)	9 (100)	18 (100)
chromaturia	25 (10)		9 (100)	66 (100)	9 (100)	18 (100)
dysuria	1 (<1)			1 (2)		1 (6)
renal pain						1 (6)
<b>Respiratory, Thoracic And Mediastinal Disorders</b>						
total	71 (29)	1(3)	0	3(5)	2(2)	3(7)
cough		1(3)				2(11)
dry throat				1(2)		1(6)
dyspnea				1(2)	1(11)	
hypoxia	35 (14)					
throat tightness				1 (2)	2 (22)	2 (11)
<b>Skin And Subcutaneous Tissue Disorders</b>						
total	21 (9)	0	0	62 (94)	9 (100)	18 (100)
erythema	2 (<1)			61 (92)	9 (100)	18 (100)
exanthema						2 (11)
hyperhidrosis					1 (11)	
pruritus				1 (2)	2 (22)	3 (17)
rash papular	1 (<1)					3(17)
skin discoloration	14 (6)					
<b>Vascular Disorders</b>						
total	45 (18)	2 (6)	0	1 (2)	0	1 (6)
circulatory collapse	13 (5)					
hot flush						1 (6)
hypertension	14 (6)					

#### 7.1.5.5 Identifying common and drug-related adverse events

From Study EML 015722-H101, the following common adverse events may be reasonably considered to be drug related, based on comparisons to placebo. Common is defined as reported in three or more subjects for an incidence of 5% or greater.

**Table 9** Common drug-related adverse events (NDA Table 2.5-6 on p. 29 of V. 2 in Mod. 2)

Adverse Event	5-g Dose Group		10-g Dose Group	
	Hydroxocobalamin (N=66) n (%)	Placebo (N=22) n (%)	Hydroxocobalamin (N=18) n (%)	Placebo (N=6) n (%)
Chromaturia	66 (100)	0	18 (100)	0
Erythema <sup>1</sup>	62 (94)	0	18 (100)	0
Rash <sup>2</sup>	13 (20)	0	8 (44)	0
Blood Pressure Increased <sup>3</sup>	12 (18)	0	5 (28)	0
Nausea	4 (6)	1 (5)	2 (11)	0
Headache	4 (6)	1 (5)	6 (33)	0
% Lymphocyte Decreased <sup>4</sup>	5 (8)	0	3 (17)	0
Injection Site Reaction	4 (6)	0	7 (39)	0

<sup>1</sup> Erythema combines events reported as “erythema” and “generalized erythema.”

<sup>2</sup> Rash combines events reported as “rash,” “rash pruritic,” “exanthema,” “rash papular,” and “rash pustular.”

<sup>3</sup> Blood pressure increased combines events reported as “blood pressure increased” and “blood pressure increased diastolic.”

<sup>4</sup> Reported as “lymphocyte count decreased.”

#### 7.1.5.6 Additional analyses and explorations

The limited variability in demographics for Study EML 015722-H101 and the limited collection of demographic information in the French studies precluded substantial explorations and additional analyses of adverse events. Where substantial differences occurred for individual events, based on gender or age, they were noted in the description of the event along with the onset and duration when the information was available.

#### 7.1.6 Less Common Adverse Events

Less common adverse events may be found in the comprehensive list of adverse events included in **Appendix 10.3**. The usefulness of the list for delineating treatment-emergent adverse events in cyanide-exposed patients is limited by the lack of comparator.

## 7.1.7 Laboratory Findings

### 7.1.7.1 Overview of laboratory testing in the development program

The Sponsor provided comprehensive testing of laboratory parameters in the safety and tolerability study (EML 015722-H101). The logistics of the testing are described in detail in the review of the study included in the appendix. Laboratory assessments of patients treated with hydroxocobalamin in the French studies were based on clinical indication rather than protocol specifications. Without a comparator and with only limited data confounded by the patients' presenting conditions, the usefulness of this information is limited.

A key requirement for the NDA submission was that the Sponsor assess for interference of cobalamins-(III) with automated laboratory equipment. The table below is copied from the NDA and indicates which measurements are affected and the magnitude and direction of the interference.

**Table 10** Laboratory interference with hydroxocobalamin (Table 2.5-9 on p.35; Vol. 2; Mod. 2)

Laboratory Parameter	No Interference Observed	Artificially Increased $\geq 10\%*$	Artificially Decreased $\geq 10%*$	Unpredictable	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 (interference lasted up to 4 days)
Hematology	Erythrocytes Hematocrit MCV Leucocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets	Hemoglobin MCH MCHC Basophils			12-16 hours
Coagulation				aPTT PT INR	24-48 hours

\*based on measurements observed on at least one analyzer.

### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons for laboratory values were available only from Study EML 015722-H101, which assessed safety and tolerability when Cyanokit was administered to healthy adults who were not exposed to cyanide. The limited laboratory data available from the uncontrolled French trials were evaluated in the context of the findings from Study EML 015722-H101; however, the exposure of the patients in these studies to cyanide and other toxins, as well as possible injuries, precluded discernment of treatment-related laboratory abnormalities.

### 7.1.7.3 Standard analyses and explorations of laboratory data

Clinical laboratory evaluation included hematology, coagulation profile, biochemistry, arterial and capillary blood gas analyses and urinalysis including sediment. Because the study was not powered to assess differences in safety parameters between OH-Co and placebo treatments, only descriptive statistics were provided, as agreed to in discussions between the Sponsor and the Division regarding design of the study. As hydroxocobalamin is dark red in color and water soluble, there was concern that its presence in a blood specimen could interfere with the determination of laboratory parameters. The Sponsor evaluated the presence and extent of interference for each laboratory parameter on various automatic analyzers prior to the study and reported their findings in the NDA. Those methods showing the least interference from OH-Co were used for this study. Interference is described below for each laboratory parameter that was affected by hydroxocobalamin.

Analyses conducted by the Sponsor and confirmed by this reviewer included comparison of the means across treatment groups and over time, evaluation of shift tables for trends, and evaluation of outliers for each parameter.

#### 7.1.7.3.1.1 Biochemistry

According to the Sponsor, the following parameters appeared to have systematic changes that were OH-Co-dose related: creatinine, total bilirubin, inorganic phosphate, GPT, ALT and amylase. However, these same parameters were also associated with OH-Co-induced interference during *in-vitro* testing, which was, according to the Sponsor, in the same direction and of similar magnitude as that observed *in vivo*. Thus, it is uncertain whether the measured values reflect true abnormalities, and if so, what the actual extent and the significance of the abnormalities are. The findings for all assessed biochemistry parameters are described below.

#### Renal Function

Mean creatinine concentrations increased slightly from baseline between 2 and 12 hours post-treatment for all subjects receiving OH-Co. The maximum mean increase was 8.7  $\mu\text{mol/L}$  (12.4%), which occurred at 2 hours in the 10-g dose group. The subjects receiving placebo tended to have slight decreases of this parameter during the same time period. The devices used

to measure creatinine levels were found to be affected by OH-Co such that the results would be expected to be elevated, based on *in-vitro* evaluations. The Sponsor indicated this could account for much, if not all, of the difference. Regardless of interference, the means for each sex were within normal limits for all time points and OH-Co-dose groups. Review of the individual results indicated 29 values that were outside the range of normal limits. Of these, nine were in the placebo group. The OH-Co-related values included 8 values that were below and 12 that were above the normal limit range (45.0-84.0  $\mu\text{mol/L}$  for females and 59.0-104.0  $\mu\text{mol/L}$  for males); all were < 10  $\mu\text{mol/L}$  outside the range of normal. There was no apparent pattern as to when the outliers occurred or to which dosage group they belonged.

Urea levels were not significantly affected by treatment with OH-Co compared to placebo. There appeared to be no trends for changes in the mean with respect to either the dose of OH-Co or time following administration. All mean concentration values were well within normal limits (0 mmol/L-8.30 mmol/L). In all, six subjects had measurements that exceeded the upper limit of normal; two of those subjects were treated with placebo. Of those treated with OH-Co, one subject received a 2.5-g dose and had a maximum urea value of 8.51 mmol/L 12 hours after the infusion; two subjects who received a 5-g dose also had maximal urea values (8.36 mmol/L and 8.55 mmol/L) at 12 hours following the infusion; one subject had a maximal value of 9.73 mmol/L on Day 8 after receiving 5 g of OH-Co.

#### Electrolytes

Mean sodium concentrations were observed to decrease slightly at 2 hours following the 7.5-g and 10-g doses of OH-Co. The maximal mean decrease for sodium, compared to the baseline value, in the OH-Co-treated subjects was 2.18 mmol/L (1.57%), which occurred in the 10-g treatment group; whereas the maximal decrease for placebo treatment was 0.89 mmol/L, which occurred following the 7.5-g placebo treatment. Other than this observation, no systematic increase or decrease in the mean sodium values were observed for either treatment group, and the mean values were within normal limits at all time points for all treatment groups. All 32 of the placebo outliers occurred in 14 subjects and ranged from 133.6 mmol/L to 135.9 (normal range: 136.0 mmol/L-145.0 mmol/L). Three of the OH-Co-treated subjects had a single elevated sodium level ranging from 146.7 mmol/L to 149.3 mmol/L, and 88 incidents of low sodium levels ranging from 132.6 mmol/L to 135.9 mmol/L were reported for 45 subjects, 31 of whom received a 5-g dose.

Mean potassium levels for all treatment groups were 0.3 mmol/L to 0.6 mmol/L less at Baseline than at Screening. The levels then began on Day 2 to trend upwards and return to Screening levels by Day 28. There were no marked differences between treatments or dosing arms. There were 59 outliers; four of which were below and 55 of which were above the reference limits of normal (3.5 mmol/L-5.1 mmol/L). The majority (27/42) of the OH-Co related outliers occurred in association with the 5-g dose; the same was true for the placebo treatment (12/17). The range for the elevated outliers was 5.11 mmol/L to 5.98 mmol/L for the placebo groups and 5.11 mmol/L to 5.70 mmol/L for the OH-Co groups. For outliers that were below the normal range, the placebo associated value was 3.45 mmol/L, and the OH-Co associated outliers included two incidents of 3.46 mmol/L and a single occurrence of 3.32 mmol/L. There was no pattern to the occurrence of the outliers relative to the time of treatment.

Mean serum **chloride** levels exhibited little change from baseline for both treatment groups and all dose groups. Subjects in the 2.5-g treatment groups had the least numbers of outliers while the outlying values that occurred in the other treatment groups appeared to be evenly distributed over time and treatment groups. There were eight incidents of low chloride levels in the placebo treatment arms. Subject 2076 had 6 chloride levels less than 98.0 mmol/L including the Baseline value; two other subjects, one each from the 7.5-g and 10-g dosing groups had low chloride levels. Fifteen subjects who received OH-Co had low chloride levels: eight from the 5-g dose group, three from the 7.5-g dose group, and four from the 10-g dose group. The chloride levels ranged from 96.1 mmol/L to 97.9 mmol/L with the single exception of a 44.2 mmol/L Day 15 measurement for Subject 3012 who received a 7.5-g dose. This subject required no therapy and otherwise had normal chloride levels. There were 16 incidents of elevated chloride levels in the placebo-treatment group which included three Screening values and one Baseline value; the range was 106.2 mmol/L to 108.6 mmol/L. Among the OH-Co-treated subjects, there were 58 incidents of elevated chloride levels that ranged from 106.1 mmol/L to 110.8 mmol/L. While the two highest measured values occurred in subjects who received a 10-g dose, there was no overall dose relationship. It was noted that 49 of the elevated values occurred between Hour 2 and Day 15 following the OH-Co infusion; however, there was no temporal pattern to the magnitude of the deviations from normal.

The mean levels of venous **bicarbonate** varied minimally from Screening and Baseline through Day 28 for both treatment arms and all dose groups. All mean levels were within normal limits (22.0 mmol/L-29.0 mmol/L). Outliers for the placebo-treated subjects included 19 measurements from 12 subjects which were above normal and ranged from 29.1 mmol/L to 31.5 mmol/L, and 42 measurements from 20 subjects which were less than normal and ranged from 17.5 mmol/L to 21.9 mmol/L. There was no pattern to the outliers either temporally or by dose.

#### Hepatic Function

**Total bilirubin** exhibited a marked increase from baseline starting at 2 hours post-dose until Day 4 after all OH-Co doses. The increases appeared to be dose dependent with the greatest increase in mean concentration of 70.0  $\mu\text{mol/L}$  (613%) at 2 hours after the 10-g dose of OH-Co. The mean values for total-bilirubin concentrations were above the reference range in all OH-Co-dose groups, whereas, the placebo-treated subjects had only minor fluctuations in their concentrations over time. The Sponsor noted that analyzer interference from OH-Co may have contributed significantly to the elevated bilirubin values. For an OH-Co concentration of 125  $\mu\text{g/mL}$ , the interference from an *in-vitro* sample biased the actual level by 66%-244%; for an OH-Co concentration of 1250  $\mu\text{g/mL}$ , the bias ranged from 685%-1317%. The PK results indicated  $C_{\text{max}}$  values for total cobalamins were 288  $\mu\text{g/mL}$  and 995  $\mu\text{g/mL}$  for the 2.5-g and 10-g OH-Co doses, respectively, suggesting the changes observed with *in-vivo* samples were due primarily to interference of the measurement by OH-Co.

**Glutamic pyruvic transaminase (GPT)**, also referred to as alanine aminotransferase (ALT), exhibited mean serum concentration decreases between 2 hours post-dose and Day 2 after all OH-Co doses. The decreases from baseline appeared to be dose-dependent with the largest mean decreases occurring with the 10-g dose and having values of 8.5 IU/L (40%) at 2 hours measured

with the Cobas Integra® analyzer and 16.2 IU/L (50%) at 4 hours post-dose with the Vitros® analyzer. Following the decrease, there was an increase in the mean GPT values, compared to baseline, starting after Day 3 and resolving by Day 28. However, this change was not dose dependent and was more pronounced with one analyzer than with the other as shown in the table below.

**Table 11** Increases in mean GPT (ALT) following initial decreases

Analyzer	OH-Co Dose (g)	Mean Change from Baseline (IU/L)	% Change from Baseline	Time Post-Dose
Cobas® Integra 700	2.5	15.4	89	Day 8
	5	6.74	38	Day 15
	7.5	12.4	52	Day 8
	10	6.5	30	Day 4
Vitros® 950	2.5	10.1	32	Day 8
	5	1.4	4	Day 15
	7.5	8.4	25	Day 8
	10	1.2	4	Day 8

The Sponsor noted that there was a nearly linear negative *in-vitro* interference for GPT with the Cobas Integra® analyzer for concentrations of OH-CO in the range of 0-1250 µg/mL. For the Vitros® analyzer, there was a divergent pattern of interference ranging from -4.3% to +16.5% at 125 µg/mL and -16.5% to +32% at 1250 µg/mL. This may account, in part, for the changes noted, but it is not clear as to what extent the interference may have biased the results.

Examination, by this reviewer, of the outliers for GPT measurements made with the Cobas Integra® analyzer indicated a preponderance of below normal values for female subjects with the 5-g and 10-g doses suggesting a gender-based difference for these results. However the opposite trend was true for the Vitros® analyzer, although not as pronounced. A comparison of the number of below-normal values for each analyzer, dose and gender is shown in the table below. Separating the male and female subjects who received OH-Co treatment and assessing mean GPT values at the time points where drops below normal limits occurred in the group means indicated that all means for male subjects were within normal limits, whereas for the female subjects there were two time points, 2 hours following the 10-g infusion and 4 hours following the 5-g infusion, that the mean values for GPT as measured by the Cobas Integra®, 7.5 IU/L and 9.4 IU/L, respectively, were below the lower limit of normal. The mean values as assessed by the Vitros® analyzer were within normal limits for both genders at the timepoints in question.

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**Table 12** Below-normal-limits outliers for GPT values between 2 and 72 hours after infusion

OH-Co Dose (g)	Number of GPT outliers below normal limits			
	Cobas Integra®		Vitros®	
	Male	Female	Male	Female
2.5	2	6	3	0
5	29	98	30	3
7.5	6	3	6	0
10	1	22	18	6

b(4)

Mean changes from baseline values in **glutaryl oxaloacetic transaminase (GOT)**, also referred to as aspartate aminotransferase (AST), did not follow a trend over time with either treatment. All mean values were within normal limits (males: 10.0 U/L-50.0 U/L; females: 10.0 U/L-35.0 U/L). There were transient increases in GOT above the upper limit of normal observed in 14 subjects; 11 of whom received OH-Co, and three of whom received placebo. For two subjects (1 OH-Co, 1 placebo), the increases were present before the infusion; for eight subjects (5 OH-Co; 3 placebo), they occurred between 2 hours post-dose and Day 4 [the Sponsor reported six subjects (4 OH-Co; 2 placebo) for this category]; for nine subjects (all OH-Co), they occurred between Day 8 and Day 28. The above-normal measurements, (19 OH-Co; 6 placebo) were generally small,  $\leq 10$  U/L over the upper normal limit. Two placebo-treatment values, including one baseline measurement were between 10 and 15 U/L over the upper limit of normal, and four OH-Co-treatment values were between 10 and 15 U/L over the upper limit of normal. Only two values were  $> 15$  U/L above the upper limit of normal; both were associated with OH-Co treatment. The first value (69.6 U/L for Subject 2011) occurred on Day 15; the other value (92.5 U/L for Subject 3010) occurred on Day 4. Both of these subjects had only the single abnormally high value.

Mean **alkaline phosphatase** and **gamma-glutamyl transpeptidase (gamma-GT)** activity levels exhibited no systematic changes from Baseline levels with time or any differences between treatment arms. Hydroxocobalamin interference in the assessment of these parameters was not reported.

Mean **cholesterol** levels showed a somewhat dose-related increase from baseline at 2 hours after the OH-Co infusions, which contrasted to small decreases observed in the placebo groups. The differences resolved by Day 3. Positive interference by OH-Co was seen for measurements of cholesterol *in vitro*. The magnitude of the interference was between 20% and 40% at 1250  $\mu\text{g/mL}$  OH-Co indicating that the changes seen *in vivo* were more likely due to interference than the action of the drug.

Mean serum **triglyceride** levels increased considerably starting at 2 hours after OH-Co infusions and remained elevated, relative to Baseline, until Day 2. The elevations were generally greater for higher doses of OH-Co as indicated in the table below. The placebo-treated subjects experienced no appreciable changes to their triglyceride levels with either time or dose received. While the elevations for the OH-Co-treated subjects were marked, the mean values were within normal limits (0 mmol/L-2.30 mmol/L) except for the 12-hour mean value of the 10-g OH-Co-

dose group, which was 2.37 mmol/L. The Sponsor indicated in Table 12.4-2 of the submission that there was positive interference by OH-Co on the triglyceride measurement, the extent of which is uncertain but appeared to be  $\geq 10\%$ . A review of the outliers indicated substantially more in the OH-Co-treated subjects than the placebo-treated subjects: 87 outliers for 32 subjects versus 26 outliers for 9 subjects, respectively, and a dose-dependent increase in the range of the outliers. Overall, the outliers ranged from 2.31 mmol/L to 8.47 mmol/L for the OH-Co-treated subjects.

**Table 13** Mean triglyceride levels from Baseline to Day 3 for subjects treated with OH-Co

Time after infusion	Mean Triglyceride Level [mmol/L] (% increase from baseline)			
	2.5-g Dose	5-g Dose	7.5-g Dose	10-g Dose
Baseline	0.85	1.01	0.75	1.05
2 h	1.14 (34)	1.49 (48)	1.40 (87)	1.95 (86)
4 h	1.26 (48)	1.59 (57)	1.46 (95)	1.96 (87)
12 h	1.73 (104)	1.95 (93)	1.51 (101)	2.37 (126)
Day 2	1.00 (18)	1.29 (27)	1.04 (39)	1.37 (30)
Day 3	1.16 (36)	1.30 (29)	0.97 (29)	1.37 (30)

#### Other Biochemical Assessments

Mean serum **glucose** concentrations showed slight decreases from baseline at 2 hours after the infusion followed by post-prandial increases in the means at four and 12 hours post-dose. The increases were observed in both the placebo and OH-Co treatment groups and were not considered clinically relevant or drug related.

Mean **total protein** levels decreased from baseline for subjects in all treatment arms between 2 and 12 hours post-infusion. Some subjects in all treatment groups had levels below the lower limit of normal during this time period. Between Day 3 and Day 28, increases in the mean protein levels were observed in all treatment groups, but at follow-up the mean concentrations were comparable to those at Screening. The changes appeared to be neither drug related nor clinically relevant.

Mean **albumin** concentrations, like mean total protein concentrations, exhibited a decrease from baseline in all treatment groups between 2 and 12 hours following the infusion. This was followed by increases in the means between Day 2 and Day 28. None of the mean albumin concentrations reached levels outside the reference range for normal, and the decreases for both albumin and total protein concentrations were attributed to a combination of dilution by the infusions and blood sampling.

No systematic changes were observed for **lactate dehydrogenase (LDH)** compared to Baseline levels for any treatment group, but a positive increase in values was reported with *in-vitro* assessment of interference.

Mean **creatinine kinase (CK)** levels exhibited no systematic changes from Baseline following study-drug infusion. There were significant elevations in CK noted for three subjects who received OH-Co: on Day 4, for Subject 1010, who received a 2.5-g dose; on Days 15 and 28, for Subjects 2011 and 2015, respectively, who received 5-g doses; and on Day 15 for Subject 3010, who received a 7.5-g dose and whose CK level was 934 IU/L; and on Day 15 for Subject 4024, who received a 10-g dose. These were all attributed to increases in physical activity or participation in sports. Subject 2024, who received a 5-g dose of placebo, also exhibited abnormally high CK on Day 1 which was similarly attributed to physical activity.

The mean **creatinine kinase isoenzyme MB (CK-MB)** levels decreased with OH-Co infusions to >1 IU/L between 2 and 4 hours post-dose for the three higher doses. These decreases were followed by rebound increases that were double the Baseline values between 12 and 24 hours post-dose. The interference assessment for this parameter indicated highly variable results that did not demonstrate a clear concentration pattern. The significance of these findings is not clear; assessments made for the placebo group showed little variation from the Baseline values.

Mean **troponin** levels exhibited no systematic changes over time and no differences between treatment arms.

Mean **amylase** activity exhibited a OH-Co dose-dependent decrease between 2 and 4 hours post-infusion, which was not observed in the placebo treatment arms. Recovery to Baseline levels occurred by 12 hours post-dose. The decrease in the mean for the OH-Co 10-g dose group observed at 2 hours post-dose was 24.9 U/L (35%) from Baseline, while the mean changes in the placebo groups ranged from -4.8 U/L to 0.5 U/L. It was noted that the decrease in amylase activity could be attributed to interference from the OH-Co, as *in-vitro* studies showed a negative interference in the range of 38% to 6% at 1.25 g/L OH-Co.

Mean concentrations of **inorganic phosphate** exhibited non-dose-related decreases from Baseline at 2 to 4 hours following the infusion of OH-Co. The greatest decrease in the mean concentration, -0.3 mmol/L (-22%) was observed 4 hours following the 7.5-g OH-Co dose. The mean concentrations of inorganic phosphate at the 2 and 4 hour time points were within 0.6 mmol/L of baseline for all the placebo groups. The Sponsor noted that OH-Co produces a negative interference of 28%-30% at OH-Co concentrations of 1.25 g/L, which could explain the changes observed in the study.

Mean **C-reactive protein (CRP)** levels increased sooner and to a somewhat greater extent with increasing doses of OH-Co. With the lowest dose, the increase appeared around Day 4 and persisted through Day 28 with a peak mean increase from baseline of 0.522 mg/L (59%). For the 5-g, 7.5-g and 10-g doses, the onset of the increase occurred at Day 2, 12 hours, and 12 hours, respectively, with peak mean increases of 1.53 mg/L (102%), 3.74 (358%), and 2.29 mg/L (189%), respectively. Relative to placebo, the changes for CRP were observed only with the 7.5-g and 10-g dose groups with peak differences occurring at Day 3; the response to the two treatments was indistinguishable between end of infusion and Hour 4 and again after Day 8. These differences can be attributed to outliers as shown in the table below.

**Table 14 Outliers for C-Reactive Protein**

Subject No. and Dose (g)	C-Reactive Protein Outlying Abnormal Values (mg/mL)								
	Baseline	2 hours	4 hours	12 hours	Day 2	Day 3	Day 4	Day 8	Day 28
2057 (5)									23.7
2066 (5)	13.6	12.0	11.5	8.9	7.0	5.4		20.2	
2072 (5)									46.1
3012 (7.5)					5.5	24.3	16.2		
4020 (10)				13.6	20.6	12.1			

For subjects 2066, 3012 and 4020, the levels of CRP normalized within three days. For subjects 2057 and 2072, the CRP levels spiked on Day 28, all other measures of CRP were  $\leq 2.6$  mg/mL and 0.6 mg/mL, respectively. The significance of this finding is uncertain; the Investigators neither attributed it to OH-Co treatment nor considered it clinically significant. CRP measurements were not affected by OH-Co interference based on *in-vitro* testing.

Mean serum levels of calcium and uric acid exhibited no systematic changes from Baseline either with time or between treatment groups.

#### 7.1.7.3.1.2 Hematology

Systematic changes from Baseline values over time or between treatment groups were not observed for **erythrocyte count, hemoglobin concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH),** and percentage of **basophils**. Changes in other parameters are described below.

The mean **white blood cell counts (WBC)** increased by as much as 47% over Baseline for all OH-Co dose groups between 2-12 hours after the infusion of study drug. Levels returned to Baseline by Day 3. There was no apparent dose-dependency to the magnitude of the change, but the highest values were observed at the 4-hour sampling for the two higher doses and at the 12-hour sampling time point for the two lower doses. The clinical significance of this finding, if any, is uncertain.

The mean **lymphocyte counts** did not change systematically or substantially from Baseline in any of the treatment groups; however, the mean lymphocyte-percentage of WBC exhibited a marked dose-dependent decrease at 4 hours post-dose. The maximum decrease, to 59% of the Baseline value, occurred in the 7.5-g OH-CO treatment arm. The mean **neutrophil counts**, in contrast to the lymphocyte counts, exhibited marked increases in both the absolute counts and percentages of WBC in a dose-dependent fashion at 4 hours after the infusion. The maximum increase, to 147% of the baseline value, also occurred in the 7.5-g OH-CO treatment arm. As with the WBC changes, the clinical significance of these lymphocyte and neutrophil findings, if any, is uncertain.

The mean percentage of **monocytes** declined between 2 and 4 hours post-dose, but the change was similar to that observed with the placebo treatments at the same time points. The mean percentage of **eosinophils** also declined during the same period compared to Baseline and to the placebo treatment arms. These changes resolved by 12 hours post-dose; however, the mean percentages for the two higher OH-Co doses increased compared to Baseline and placebo, peaking on Day 3 and resolving by Day 8.

The mean **thrombocyte** counts decreased from Baseline values, versus placebo, in the 10-g dose group starting at 2 hours post-dose and resolving by Day 3. This drop was followed by an increase compared to Baseline, but not placebo, that occurred on Day 15 and resolved by Day 28. Interpretation of these changes, which were within normal limits, is made difficult by the negative interference of OH-Co on thrombocyte measurement that was assessed as up to 12% during *in-vitro* studies.

#### 7.1.7.3.1.3 Coagulation

A consistent and dose-dependent decrease from Baseline and placebo in the mean **prothrombin time (PT)** with corresponding increases in the mean **International Normalized Ratio (INR)** and mean **activated partial thromboplastin time (aPTT)** was observed from 2-4 hours post-dose. These differences were greatest in the 10-g OH-Co-dose group with a maximum decrease in PT of 19% and maximum increases of aPTT and INR of 15% and 24%, respectively. This could be attributed in large part to the interference of hydroxocobalamin on measurements of PT and aPTT that were assessed as -4% to 143% and 1% to 56%, respectively.

#### 7.1.7.3.1.4 Urinalysis

All urinalysis parameters exhibited pronounced, dose-related increases from Baseline starting on Day 2 and resolving by Day 15. With the exception of specific gravity, there was positive interference from hydroxocobalamin, which could account for the changes observed in pH, occult blood, leukocytes, protein, glucose, urobilinogen, urinary nitrite and ketones. There was no interference data available for specific gravity.

Evaluation of the urinary sediment revealed no systematic changes for leukocytes, epithelial cells, bacteria, hyaline cases, mucus, triple phosphate, urates, and carbonate. There were, however, some hydroxocobalamin-treated subjects who had increased erythrocytes, granular casts and oxalate crystals present in their specimens. These are described below.

Five subjects given 10-g doses of OH-Co had  $\geq 10$  erythrocytes, whereas, only two subjects who received 5-g doses of OH-Co, had values  $\geq 10$  for erythrocytes.

There were five cases of granular casts noted; one in each of the 2.5-g and 5-g dose groups, and three in the 7.5 dose group. These were found at the 12-hour and Day-8 assessments. A dose-

dependent increase in oxalate crystals was also observed on Days 1, 2 and 8, but on Days 15 and 28 there were occasional findings of crystals in all OH-Co-dose groups.

#### **7.1.7.3.1.5 Arterial Blood Gases**

There were no systematic changes observed between pre-dose and post-dose and between OH-Co and placebo treatment for any blood gas parameter. It was noted that some individual values were above the normal range for partial pressure of oxygen and oxygen saturation, while others were below the normal range for partial pressure of carbon dioxide. These variations occurred both pre- and post-treatments across all treatment arms and were not clinically relevant.

#### **7.1.7.4 Additional analyses and explorations**

The limited scope of the development program and paucity of laboratory data for hydroxocobalamin use in patients precluded the conduct of additional analyses and explorations.

#### **7.1.7.5 Special assessments**

Special assessments were not performed due to the proposed conditions of use for hydroxocobalamin, i.e., it will be used acutely to treat a potentially life-threatening exposure to cyanide. The biochemistry data gathered from the healthy volunteer and French studies did not suggest that the drug alone causes toxicity as assessed by clinical laboratory evaluations.

#### **7.1.8 Vital Signs**

##### **7.1.8.1 Overview of vital signs testing in the development program**

In study EML 015722-H101, the assessment of vital signs was a key element of the protocol. At the Division's request, assessments were performed at critical prespecified time points during the protocol. Prespecified criteria, see table below, were used to discern adverse events and to classify them as clinically relevant or not. The blood pressure criteria were of particular interest because it was on the basis of changes for this parameter that the study was terminated prematurely.

**Table 15** Classification of Vital Signs (modified NDA Table 12.5-3 p. 240; Vol. 3; Mod. 5)

Parameter	Normal Range	Abnormal But Not Clinically Relevant	Abnormal And Clinically Relevant
Systolic Blood Pressure (mmHg)	90-140	Low: 60-89 High: 141-179	Low: <60 High: >179
Diastolic Blood Pressure (mmHg)	50-90	Low: 40-49 High: 91-109	Low: <40 High: >109
Pulse Rate (bpm)	50-90	Low: 35-49 High: 91-140	Low: <35 High: >140
Respiratory Rate (bpm)	14-18	Low: <14 High: >18	Not applicable
Body Temperature (°C)	36.0-37.5	Low: <36 High: 37.6-39.0	Low: not applicable High: >39
Pulse Oximetry (%)	95-100	93-95	≤92

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Only the safety and efficacy study, EML 015722-H101, had a control arm, and therefore, it was the only study considered for analysis in this section.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

The mean values of heart rate at Screening and all follow-up assessments differed only slightly and not in a dose-dependent fashion between treatment groups. A total of nine subjects had at least one heart rate ≤ 40 bpm. All of these subjects were male and had received active treatment.

Mean systolic blood pressure (SBP) increased substantially from Baseline values for subjects in each OH-Co-dose group. This was in contrast with only minor fluctuations in SBP that were observed in the corresponding placebo groups. The increases in SBP with OH-Co treatment were noted starting 5 minutes after the infusion was initiated and peaked near or at the end of the infusion. The mean SBPs returned to near-Baseline values between 4 and 8 hours following the end of the OH-Co infusion. The maximum mean changes in SBP for the treatment cohorts are shown in the table below. The mean maximum increases were similar for all OH-Co-dose groups; female subjects had, on average, slightly higher maximum mean increases than male subjects. The greatest increase in SBP was 57 mmHg and occurred five minutes into the 2.5-g OH-Co infusion for Subject 1001; the resultant SBP was 172 mmHg. For the entire study, the highest SBP observed was 198 mmHg, which was recorded for Subject 1007 three minutes after the start of a 2.5-g OH-Co infusion.

Mean diastolic blood pressures (DBP), like the mean SBPs, exhibited a marked increase from Baseline within minutes of the start of OH-Co infusions while the placebo infusions showed minimal fluctuations. The increases were noted at 5 minutes into the infusion, and peak values were observed near or at the end of the OH-Co infusions. Increases in DBP were similar for the

two higher OH-Co doses, which were greater than that of the two lower doses both of which were similar to each other. The DBP values declined when the OH-Co infusion was terminated and returned to Baseline values over the following 4 hours. DBP remained low for the remainder of the 24-hour monitoring period. The maximal individual increase in DBP was 52 mmHg with a resultant 114 mmHg DBP 15 minutes into the infusion of a 5-g dose of OH-Co for Subject 2026. The overall maximal DBP occurred 10 minutes after the start of a 5-g OH-Co infusion for Subject 2068 who had a DBP of 133 mmHg recorded at that time. Female subjects were noted to have higher mean maximum increases in DBP than the male subjects.

The mean arterial blood pressure (MAP) was calculated for all time points at which SBP and DBP were available. The baseline MAP was calculated using the median SBP and DBP for the values measured at 60, 40 and 20 minutes prior to the start of study-drug infusion. As would be expected from the findings for SBP and DBP, there was a marked increase in MAP during OH-Co infusion. MAP returned to near-Baseline levels by four hours after the infusion was complete. MAPs remained at the Baseline levels for the remainder of the 24-hour monitoring period. Only marginal changes from Baseline were observed for placebo-treated subjects during the same time period. Among subjects receiving OH-Co infusions, female subjects were found to have higher maximal MAPs than male subjects.

**Table 16** Summary changes in blood pressure (based on Table 12.5-2 on page 239 of Volume 3 of Module 5 of the NDA).

Parameter	2.5-g Dose		5-g Dose		7.5-g Dose		10-g Dose	
	OH-Co n=9	Placebo n=3	OH-Co n=66	Placebo n=22	OH-Co n=9	Placebo n=3	OH-Co n=18	Placebo n=6
Systolic blood pressure (mmHg)								
Maximum mean change from Baseline	32	3	23	0	27	7	26	4
SD	19	7	17	6	10	8	13	-2
Range	0-57	-4-11	-28-54	-13-16	14-41	1-16	4-46	-2-20
Diastolic blood pressure (mmHg)								
Maximum mean change from Baseline	14	-3	18	2	25	3	23	4
SD	8	14	10	4	5	6	10	4
Range	2-30	-14-13	-8-52	-4-11	18-33	-2-10	7-38	0-10
Mean arterial pressure (mmHg)								
Maximum mean change from Baseline	17	-1	19	-1	26	4	24	-5
SD	11	13	11	4	6	7	11	4
Range	1-39	-11-13	-24-41	-11-5	19-33	-1-12	6-38	2-12

Body temperature was not markedly affected by infusion of OH-Co compared to placebo. The main effect observed was a slight decrease in mean temperature (approximately 0.5° C) for the two higher OH-Co-dose groups noted at 10 minutes after the end of the infusion and resolving by 8 hours. The change was not observed in the placebo group and, therefore, was not likely due to the infusion of a large volume of room temperature fluid.

Respiratory rate did not change in a systematic manner over time with any of the treatment arms. There were no clinically relevant changes observed among individual subjects for this parameter.

Mean changes in hemoglobin oxygen saturation as monitored by pulse oximetry did not show any trend over time. There were no marked differences between treatments for this parameter. Individual values ranged from 94% to 100% for OH-Co-treated subjects and from 93% to 100% for placebo-treated subjects.

#### **7.1.8.4 Additional analyses and explorations**

None were indicated, and none were performed.

### **7.1.9 Electrocardiograms (ECGs)**

#### **7.1.9.1 Overview of ECG testing in the development program**

ECG assessments in the animal studies indicated that no clinically relevant changes from baseline occurred following administration of hydroxocobalamin or cyanocobalamin. In Study EML 015722-H101, ECG testing was conducted at Screening, Baseline, 30 minutes and 1, 2, 4, 6, 8 and 12 hours after the study drug was infused.

#### **7.1.9.2 Selection of studies and analyses for overall drug-control comparisons**

Only Study EML 015722-H101 included a comparator and, therefore, was the only study evaluated for treatment-emergent ECG changes.

#### **7.1.9.3 Standard analyses and explorations of ECG data**

The sponsor evaluated the PR, QRS, QT and QT<sub>C</sub> intervals at Screening, Baseline and for 24 hours following the end of the infusion of study drug. There were no systematic changes noted in any of the treatment arms over time or between treatment arms for the different dosing cohorts. The mean uncorrected QT intervals were slightly different for all dosing cohorts with the OH-Co arms having intervals that were 10-20 msec longer than that of placebo for the period between baseline and 4 hours post-infusion. This difference did not exist when the corrected QT values were compared.

Among the interval changes noted for individual subjects, none constituted an adverse event, and from the Investigator's perspective, none were considered clinically significant. There was no trend toward an increase in abnormal ECG findings with increasing dose of OH-Co. Abnormal findings, although not clinically relevant, tended to occur between the baseline and 1-hour post-dose time points. The abnormal findings were not consistently related to particular subjects;

rather isolated abnormalities were noted for different subjects at different time points. The Sponsor indicated that the type and frequency of abnormal findings in individual subjects across active- and placebo-treatment groups did not show any relevant difference. There were no dose-, age- or sex-related dependencies for any of the ECG abnormalities.

#### 7.1.9.4 Additional analyses and explorations

None were indicated, and none were performed

#### 7.1.10 Immunogenicity

**b(4)**

Cyanokit is intended for acute use in life-threatening situations. Additionally, it contains no \_\_\_\_\_ or \_\_\_\_\_; therefore, it is not expected to elicit an immunogenic response, and an evaluation of immunogenicity has not been performed.

#### 7.1.11 Human Carcinogenicity

The active ingredient of Cyanokit is hydroxocobalamin, a precursor to Vitamin B<sub>12</sub>. When administered to patients suffering from cyanide poisoning, hydroxocobalamin binds with cyanide to form cyanocobalamin, Vitamin B<sub>12</sub>. Although a tumor promoting effect (hepatomas) of Vitamin B<sub>12</sub> has been reported in a rat study (Day *et al.*, 1950) there are no reports attributing carcinogenic potential to cyanocobalamin in humans when used to treat Vitamin-B<sub>12</sub> deficiency. The doses of both hydroxocobalamin and cyanocobalamin (when there has been exposure to cyanide) are more than 1,000 fold greater than the doses used to treat Vitamin-B<sub>12</sub> deficiency. It is not known whether acute, i.e., one time, exposure to such a high dose alters the risk of carcinogenicity.

#### 7.1.12 Special Safety Studies

The Sponsor was asked to conduct several animal studies to address issues which arose during the development program. These studies are listed below and are described in detail in the pharmacology-toxicology review.

1. A safety and tolerability study of high dose cyanocobalamin was to be conducted to address the concern that victims of cyanide poisoning who are treated with Cyanokit will be exposed to high blood levels of cyanocobalamin. This study was to assess whether such levels pose special safety risks to the victims and characterize the time course for when such risks arise.
2. A study of the effects of hydroxocobalamin on blood pressure in dogs was to be conducted to evaluate whether the dog model accurately reflects human response to hydroxocobalamin therapy. This study was requested after the human safety and

tolerability study revealed significant increases in blood pressure following hydroxocobalamin administration to healthy volunteers with no cyanide exposure.

3. A study assessing the dermatological effects of hydroxocobalamin in animals was to be conducted after the healthy human subject study revealed that non-cyanide exposed volunteers developed bright red coloration of the skin and multiple types of rashes following the administration of hydroxocobalamin. Phototoxicity was to be evaluated in this study

#### **7.1.13 Withdrawal Phenomena and/or Abuse Potential**

There was no indication from the clinical trials that hydroxocobalamin produced either mind-altering or mood-altering effects that would make it a potential substance of abuse. There was no evidence of a withdrawal phenomena following its use in the safety and tolerability study.

#### **7.1.14 Human Reproduction and Pregnancy Data**

The only human reproduction or pregnancy data available come from the trials reported in the NDA and included the following incidents of hydroxocobalamin exposure during pregnancy.

A single subject (Subject 2012) enrolled in Study EML 015722-H101 was reported to be pregnant on December 17, 2004. She had received a 5-g dose of hydroxocobalamin on November 15, 2004 following a negative urine pregnancy test. Her gynecologist estimated her to be in the fourth week of gestation at the time she received the study drug. The subject was followed until she delivered a healthy baby on \_\_\_\_\_

**b(6)**

In the Baud-3 study, Patient #137 was a 28-year old woman who was 18 weeks pregnant at the time she tried to commit suicide by ingesting potassium cyanide. Her medical history was significant for an extra-uterine pregnancy the year prior to admission, severe depression, and the suspicion that fetal demise had occurred with her current pregnancy. She was found convulsing and went into a coma when rescuers arrived. Her blood toxicology screen was positive for benzodiazepines. Her treatments included 10 g of OH-Co and two 8-g doses of sodium thiosulfate. Sonogram revealed a dead fetus. The Sponsor indicated that the fetal demise was thought to have occurred prior to the suicide attempt and subsequent rescue efforts.

#### **7.1.15 Assessment of Effect on Growth**

No assessments were made.

### 7.1.16 Overdose Experience

Overdose in the administration of hydroxocobalamin may best be defined as the amount of drug administered in excess of that required to bind cyanide present in the blood. However, the short half-life of cyanide in blood and the relatively long time required to measure blood cyanide levels make precise dosing nearly impossible. In a situation where excess hydroxocobalamin is present, it is possible that the patient would exhibit blood pressure responses similar to those seen in Study EML 015722-H101, i.e., increases in systolic and diastolic pressures. There is a suggestion of such a response in some of the French study data, but without a comparator and the frequent use of other supportive therapies such as volume expanders and adrenergic agonists, it is not possible to draw conclusions.

The inability to determine a precise dose, the overall tolerability observed in Study EML 015722-H101, and the dire consequences of untreated cyanide poisoning suggest that erring on the side of excessive dosing is preferable to underdosing or slowly titrating to effect.

### 7.1.17 Postmarketing Experience

Cyanokit was granted marketing authorization in France on September 16, 1996. Since that time all adverse events that have been reported to the Corporate Pharmacovigilance Department of Merck Santé have been stored in the Global Pharmacovigilance Database for the Merck Group.

Through September, 2006, there have been six spontaneous postmarketing adverse event reports filed; three were considered by the Sponsor to be serious, and three were classified as non-serious.

1. Case #6011802 reported the death of an 18-week-old fetus. The mother attempted suicide by taking potassium cyanide (she is Subject 137 in Baud Study 3). The mother also took benzodiazepines during early pregnancy. Fetal demise was ascertained after the mother was resuscitated with hydroxocobalamin and sodium thiosulfate. The report indicated that there was suspicion of fetal demise prior to the potassium cyanide intoxication.
2. Cases #6013055 and #6011519 involved allergic reactions. The first involved a patient who suffered skin eruptions and angioneurotic edema. This case was classified as serious. The second involved urticaria and was classified as non-serious.
3. Two cases were related to kidney transplantation procedures. In the first, #6006008, a female victim of cyanide poisoning who died despite resuscitation efforts and the infusion of 10 g of hydroxocobalamin underwent surgery as an organ donor to have her kidneys harvested. At the time of harvest, the donor's skin was noted to be red colored and both kidneys were noted to have a deep blue discoloration that was assessed as probably related to hydroxocobalamin. The second case, #6006009, involved the recipient of one of the harvested blue kidneys. This patient was subsequently found to have an elevated serum level of Vitamin B<sub>12</sub>, chromaturia, elevated transaminase levels and an elevated CK level. The increased Vitamin B<sub>12</sub> level was assessed as highly

probably related to hydroxocobalamin administration to the donor; the other events were considered to be possibly related to the hydroxocobalamin, but they may have also been due to the transplantation surgery.

4. The last case, #6013045, involved the administration of a 2.5-g dose of hydroxocobalamin to a 9-month old girl. The patient weighed 10 kg; therefore, the dose was excessive compared to the French-label recommendation of 70 mg/kg. No adverse reaction or patient outcome was reported.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Study EML 015722-H101 was the primary source of clinical data for the assessments of safety. It was the only study that included a comparator arm; however, the lack of subject exposure to cyanide precludes evaluation under conditions of clinical use and the assessment of risk involved with exposure to high doses of cyanocobalamin that would occur when patients exposed to cyanide are treated with hydroxocobalamin. The French studies were evaluated for the risks that could not be assessed in the safety and tolerability study. These, however, lacked a comparator arm and were of limited value as were case reports found in the literature.

#### 7.2.1.1 Study type and design/patient enumeration

The following table summarizes the study designs, doses, and numbers of subjects exposed in the studies used to assess safety.

**Table 17**

Study	Design	Number of Subjects	Doses of OH-Co evaluated (grams)	Number of OH-Co-exposed subjects
EML 015722-H101	Prospective, randomized, placebo-controlled, double-blinded, dose-escalation	136	2.5	9
			5	66
			7.5	9
			10	18
Baud-1	Prospective, open-label, uncontrolled	69	4-15	69
Baud-2	Retrospective, open-label, uncontrolled	61	2.5-15	61
Baud-3	Retrospective, open-label, uncontrolled	14	5-20	14
Fortin	Retrospective, open-label, uncontrolled	101	1-10	101

### 7.2.1.2 Demographics

The table below provides the demographic data available. In EML 015722-H101, all but one subject was Caucasian. Ethnicity data was not captured in any of the French studies.

As indicated by the table, the safety, tolerability and pharmacokinetic data derive from a nearly even mix of male and female subjects in the 18-65 year-old age group. Overall, the representation of males and females is even. While most of the patients were adults ages 18-64 years old, there is a substantial amount of data available for patients over the age of 65 years and even over the age of 75 years.

**Table 18 Overall demographics**

Study	Gender		Age (years)				
	Male	Female	Unknown	<18	≥18 and <65	≥65 and <75	≥75
EML 015722-H101	69	67			136		
Baud-1	33	36			54	5	10
Baud-2	30	31	2		41	10	8
Baud-3	12	2		1	13		
Fortin	53	48	3	8	71	6	13
<b>Totals</b>	<b>197</b>	<b>184</b>	<b>5</b>	<b>9</b>	<b>315</b>	<b>21</b>	<b>31</b>

### 7.2.1.3 Extent of exposure (dose/duration)

The duration of the hydroxocobalamin infusions for both the safety and PK populations were as shown in the table below. With the exception of one subject (Subject #4018), all received the protocol-specified dose. Subject 4018 was scheduled to receive 10 g of OH-CO, but the infusion was discontinued after 11.9 minutes (3.9 g) due to adverse reactions. All but four subjects received their infusions within 2 minutes of the specified duration, i.e., at a rate of 13.3 mL/min, which is equivalent to 333 mg/min.

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**Table 19** Duration of hydroxocobalamin infusions

Population	Statistic	OH-Co Dose							
		2.5 g OH-Co		5 g OH-Co		7.5 g OH-Co		10 g OH-Co	
		OH-Co	Placebo	OH-Co	Placebo	OH-Co	Placebo	OH-Co	Placebo
Safety	n	9	3	66	22	9	3	18	6
	Mean (SD)	8.2 (2.2)	7.5 (0.0)	15.1 (0.5)	15.1 (0.4)	22.7 (0.4)	22.5 (0.1)	29.1 (4.3)	30.2 (0.3)
	Median	7.5	7.5	15.0	15.0	22.6	22.6	30.0	30.1
	Range	7.5-14.0	7.5-7.5	14.7-18.2	14.9-17.0	22.5-23.9	22.4-22.6	11.9-30.8	30.0-30.7
PK	n	9	N/A	12	N/A	9	N/A	11	N/A
	Mean (SD)	8.2 (2.2)	N/A	15.0 (0.1)	N/A	22.7 (0.4)	N/A	30.1 (0.1)	N/A
	Median	7.5	N/A	15.0	N/A	22.6	N/A	30.0	N/A
	Range	7.5-14.0	N/A	14.7-15.1	N/A	22.5-23.9	N/A	30.0-30.5	N/A

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Four studies were conducted in France to provide information on the safety and efficacy of Cyanokit when used to treat patients who were smoke-inhalation victims or exposed to cyanide secondary to a suicide attempt or industrial exposure. These included the Baud Studies 1, 2 and 3, and the Fortin Study. None of the studies included a comparator and only one, Baud Study 1, was prospective. The Sponsor obtained the original data for these studies and supplemented it with data obtained retrospectively by searching patient medical records and emergency medical service records.

Literature reports of the use of Cyanokit were included when patient data was provided in a manner that permitted inclusion in the safety database.

### 7.2.2.1 Other studies

No other studies were submitted for consideration in the review process.

### 7.2.2.2 Postmarketing experience

There have been several reports of adverse events and death associated with Cyanokit use in Europe that have been reported to the Sponsor and are described elsewhere in this review. The reports all involved patients who were suspected of suffering from toxic effects of cyanide and possibly other substances. None of the reports raised a safety concern not already raised by the studies submitted assessing hydroxocobalamin safety and tolerability or its use in instances of suspected cyanide poisoning.

### **7.2.2.3 Literature**

The Sponsor submitted 107 publications related to hydroxocobalamin, cyanide poisoning, and cyanide antidotes. Most of these have been previously reviewed by the Division following our own literature search on the topics. The literature was reviewed with the intent of identifying safety concerns associated with the use of hydroxocobalamin which were not detected in the animal or human studies submitted; none were found.

### **7.2.3 Adequacy of Overall Clinical Experience**

The number of subjects exposed to hydroxocobalamin in the safety and tolerability study was adequate to identify a maximum tolerated dose, characterize the safety profile for non-cyanide exposed individuals, and determine the pharmacokinetic profile. The design of the study was appropriate to address the critical issues discussed at meetings during product development. The evaluation of only healthy patients in the study was a limitation; however, inclusion of more vulnerable subjects, i.e., the elderly and those with severe underlying medical problems, could not be justified from an ethical standpoint when there was no potential benefit from study participation.

The open-label French studies were seriously limited in their usefulness by the lack of some type of comparator arm. The retrospective design of three of the four studies was a further limitation to their usefulness. Nonetheless, these studies provided an opportunity to assess whether safety concerns observed in non-cyanide exposed subjects existed for cyanide-exposed patients as well. They also permitted a limited opportunity to assess efficacy.

### **7.2.4 Adequacy of Special Animal and/or In Vitro Testing**

Preclinical testing was adequate to assess QT prolongation potential, the effects of high-dose cyanocobalamin on safety, the nature of hydroxocobalamin-induced hypertension, and the effects of hydroxocobalamin on skin. These were the key issues the Division requested the Sponsor to evaluate during the development program.

### **7.2.5 Adequacy of Routine Clinical Testing**

The monitoring of laboratory parameters, vital signs, electrocardiograms, and changes in the physical examination parameters was adequate in the healthy volunteer study to capture sufficient data for a safety assessment of the use of hydroxocobalamin in patients who were not exposed to cyanide. The Sponsor also assessed for interference caused by the intense red color of hydroxocobalamin on the measurement of clinical laboratory parameters using multiple devices commonly available in hospital laboratories.

The four uncontrolled French studies assessing the use of Cyanokit in treating patients included some clinical testing; however, it is not adequate for an assessment of safety.

#### **7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup**

Hydroxocobalamin and cyanocobalamin are excreted unchanged in the urine. Hydroxocobalamin clearance was adequately addressed in the safety study. Clearance of cyanocobalamin and drug-drug interactions were not addressed and were not considered essential to take regulatory action on a potentially life-saving antidote that is administered only acutely and in situations where a patient is in extremis. There are reports that hydroxocobalamin is dialyzable, which is an important consideration should a patient with renal failure receive treatment whether or not actually poisoned by cyanide.

#### **7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

The evaluation for potential adverse events associated with hydroxocobalamin was thorough for its use as a new drug and compared to safety assessments made for sodium thiosulfate, the only approved cyanide antidote. Pending the findings of the CRISIS-I and CRISIS-II studies, there are no recommendations for further study at this time.

#### **7.2.8 Assessment of Quality and Completeness of Data**

The data submitted for the safety review included for all parameters: safety data tables with raw data, shift tables, tables of median changes from baseline, tables of frequency of outliers, and, for some parameters, plots of mean values with standard deviations as functions of time. These data allowed a comprehensive assessment of safety. By way of quality assurance, raw data from some parameters were used to confirm computed values, i.e., means, medians, and standard deviations, submitted by the Sponsor.

#### **7.2.9 Additional Submissions, Including Safety Update**

The Sponsor resubmitted several data tables after making format changes to allow easier analysis. Also submitted were responses to multiple questions concerning the data sets and study results, and the required safety update. Information from all of these submissions was incorporated into the pertinent safety evaluations.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

There were four adverse events considered important and treatment-related. Each is reviewed in more detail elsewhere in this section, but in summary they are:

1. Allergic reactions. These appear to be rare but may have life-threatening consequences. Considering the indication for hydroxocobalamin also involves a life-threatening condition, the benefit of the drug likely outweighs the risk of an allergic reaction which can be effectively dealt with by careful monitoring and aggressive therapy.
2. Hypertension. Primarily a result of increased diastolic pressure that occurs when hydroxocobalamin is administered to non-cyanide exposed patients, treatment-emergent hypertension is an adverse event that may be detected with simple monitoring and readily treated should it occur. As most victims of cyanide poisoning experience cardiovascular insufficiency and shock, the pressor effect of hydroxocobalamin was observed more often to restore normal hemodynamic parameters than noted as an adverse event. An increase in blood pressure early in the treatment of suspected cyanide poisoning should lead to a reconsideration of the differential diagnosis.
3. Erythema. The intense red coloring of the skin that occurs shortly after hydroxocobalamin administration is begun is due primarily to the color of the drug substance itself. While the coloration of the skin is not associated with any toxic findings or discomfort, the concomitant coloration of the serum has significant impact on the laboratory assessment of several biochemical and hematological parameters, which may adversely affect the ability to monitor patients who have concomitant illnesses or who have suffered additional insults related to their cyanide exposure.
4. Chromaturia. The intense red coloring of the urine, like the erythema, is due to the color of the drug substance. It too is not toxic, causes no discomfort and may interfere with clinical laboratory assessment.

### **7.4 General Methodology**

#### **7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

##### **7.4.1.1 Pooled data vs. individual study data**

Pooling was done for the French studies, which all evaluated cyanide-exposed patients. The safety and tolerability study was considered separately as it included only non-cyanide exposed individuals.

##### **7.4.1.2 Combining data**

For the French studies, the populations and the adverse event counts were simply combined. As the studies had no comparator arms, were conducted prior to seeking marketing approval in the

United States, and were designed without input from the Agency or the Sponsor, no weighing methods were utilized; the simple combination of data sets was considered the most appropriate approach.

## **7.4.2 Explorations for Predictive Factors**

Exploration for gender-related predictive factors for the different adverse events found none to exist. Limitations imposed by study designs and the nature of the indication precluded further meaningful exploration.

### **7.4.2.1 Explorations for dose dependency for adverse findings**

Study EML 015722-H101 was designed to evaluate dose dependency of adverse reactions and they are described elsewhere in this section of the review.

### **7.4.2.2 Explorations for time dependency for adverse findings**

Study EML 015722-H101 was also designed to evaluate time dependency of adverse reactions and they are described elsewhere in this section of the review.

### **7.4.2.3 Explorations for drug-demographic interactions**

Study EML 015722-H101 allowed drug-demographic interactions to be assessed only for gender. Race and age were too homogeneous in Study 015722-H101 to assess any interactions. The French studies allowed for age and gender interactions to be assessed, but lacked a comparator to put the findings into context.

### **7.4.2.4 Explorations for drug-disease interactions**

Due to the indication for treatment and the risk imposed on subjects with underlying disease, data that would allow for this type of exploration were not collected.

### **7.4.2.5 Explorations for drug-drug interactions**

Due to the indication for treatment and the risk imposed on subjects with underlying disease requiring ongoing therapy, data that would allow for this type of exploration were not collected.

### **7.4.3 Causality Determination**

The design of Study EML 015722-H101 permitted comparison of hydroxocobalamin with placebo for adverse event causality determination. In addition, the same study permitted an evaluation of causality based on dose-related changes in severity. While this permitted causality determination for hydroxocobalamin-related adverse events in a non-cyanide exposed population, the French studies provided the only information on adverse events that were associated with hydroxocobalamin use in cyanide-exposed patients. Unfortunately, these studies lacked comparator arms and did not assess multiple doses in a protocol-specified fashion. Therefore, causality determination in this population was more difficult and relied heavily on the occurrence of similar events in Study EML 015722-H101.

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## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The use of a 5-g starting dose of hydroxocobalamin reflects an appropriate tradeoff between efficacy, as demonstrated in the dog study, and safety, based on Study EML 015722-H101. The requirement that the 5-g dose be administered over 15 minutes permits an opportunity to assess for the most potentially life-threatening adverse events, allergic reaction and hypertension, and for the need for additional dosing based on patient response to treatment. Should an allergic reaction or hypertension occur, immediate discontinuation of the hydroxocobalamin infusion is the recommended first line of treatment and may limit the extent of the adverse reaction.

The studies conducted in support of dosing adequately addressed acute administration of a single therapeutic dose ranging from 5 to 10 grams in response to acute poisoning. Not evaluated were the following:

- Pediatric dosing requirements
- Dosing for continuing systemic cyanide exposure as would occur following ingestion or transdermal exposure to the poison.

### 8.2 Drug-Drug Interactions

Drug-drug interactions were not assessed. Some of the French study data suggest that restoration of normal cardiovascular status following hydroxocobalamin treatment may exaggerate patient responses to other agents administered for resuscitative purposes. Without a comparator arm, the ability to assign causality to hydroxocobalamin is lacking. As patients may be exposed to numerous toxins other than cyanide, particularly those who are victims of smoke inhalation, additional therapeutic interventions will often be required. Testing for drug-drug interactions in humans is not ethically feasible, and animal testing may not provide results that are readily transferable to humans. From a clinical perspective, one approach to deal with this situation is the use of short-acting drugs that permit rapid titration to effect until the patient has been stabilized and definitive therapy can be safely instituted.

A separate, but important, issue is drug compatibility. In the emergency setting, multiple drugs or blood and blood products may have to be administered through a single intravenous access site. Although the French studies did not report any incompatibilities, a Phase-4 commitment assessing the compatibility of hydroxocobalamin with the most frequently administered resuscitation drugs and blood products is warranted.

### **8.3 Special Populations**

Dosing in special populations was not assessed; however, the life-threatening potential of cyanide poisoning warrants early intervention and aggressive therapy. Therefore, the proposed initial dosing is appropriate for virtually the entire adult population.

### **8.4 Pediatrics**

It is anticipated that the pediatric population will be treated for cyanide poisoning at a frequency similar to that of adults, and to this end, the Sponsor has expressed interest in pursuing a pediatric indication. The following path forward is recommended following approval:

1. Pediatric development should be deferred while the Sponsor and the Agency negotiate the requirements for meaningful labeling of hydroxocobalamin for use in the pediatric population.
2. Pediatric use in the postmarketing period should be captured in the CRISIS-2 study or its equivalent.
3. Juvenile animal studies should be designed to determine appropriate dosing parameters by assessing safety in the context of efficacy.
4. Once the label has been updated to include pediatric dosing, additional postmarketing data should be collected in this population and compared to that previously collected in an attempt to discern any untoward safety or efficacy signals.

### **8.5 Advisory Committee Meeting**

The input from an advisory committee was not required during the development stages of this drug product or during the review process.

### **8.6 Literature Review**

A review of the literature, both that provided by the Sponsor and one conducted independently, revealed only a few case reports of hydroxocobalamin use suggestive of efficacy and not suggesting any safety issues not raised by the human studies. There was also additional animal efficacy information. These are addressed elsewhere in this review and the Pharmacology-Toxicology review. One study that warrants special attention and is discussed below.

Cottrell et al. (1978) investigated the use of hydroxocobalamin in preventing cyanide intoxication from infusions of sodium nitroprusside (SNP). In the study, 14 adults scheduled to undergo surgery requiring induced hypotension were randomly assigned to one of two groups:

Group 1 received only nitroprusside; Group 2 received nitroprusside and a hydroxocobalamin infusion (1 mg/mL concentration at 25 mL/hr). The patients were sedated, paralyzed and mechanically ventilated in a protocol-specified manner. Arterial blood was sampled for blood gas analyses, and red blood cell and plasma cyanide level measurements every 30 minutes during nitroprusside infusion, then every hour for four hours and then every three hours for 12 hours after the drug was stopped. The hydroxocobalamin infusion was to be administered continuously with the SNP infusion. The table below summarizes the results of the study.

**Table 20** Results of Cottrell et al. study

Group	Total dose of SNP (mg)	Red blood cell cyanide level (µg/100mL)		Plasma cyanide level (µg/100mL)	
		Baseline	Peak*	Baseline	Peak*
1	44±12	9.8±1.4	83.4±23.1	1.1±0.4	3.5±1.0
2	45±10	6.1±0.7	33.2±17.3	1.0±0.9	2.2±0.7

\* Significantly different at a level of  $p < 0.05$ .

It was noted that four patients from Group 1 had base deficits greater than -5; whereas, two patients from Group 2 had similar base deficits and red blood cell cyanide levels  $> 75 \mu\text{g/mL}$  when the hydroxocobalamin infusion was terminated before the SNP infusion.

This human, randomized, placebo-controlled study is important in that it demonstrates hydroxocobalamin significantly reduces blood and intracellular (erythrocyte) levels of cyanide, and it provides evidence that hydroxocobalamin offers the clinical benefit of reducing acid-base imbalance associated with cyanide. Although this information was not essential for a determination of safety or efficacy for hydroxocobalamin, and the dosing was not the same as proposed for cyanide poisoning, it offers relatively strong support for the findings of both safety and efficacy.

## 8.7 Postmarketing Risk Management Plan

The Sponsor proposed a Risk Management plan that included routine pharmacovigilance to capture serious adverse events associated clinical studies or reported spontaneously. In addition, the Sponsor has proposed to conduct two studies: CRISIS 1 and CRISIS 2. CRISIS 1, "Cyanide's Role in Smoke Inhalation," will document blood cyanide levels in adult smoke inhalation patients as well as the acute clinical outcomes of adult patients with smoke inhalation and suspected cyanide poisoning. The proposed study is designed as a multi-center, observational study of 50 patients who do not receive hydroxocobalamin treatment but undergo clinical and laboratory evaluations. This study is to be completed prior to the approval of hydroxocobalamin, thereby avoiding any ethical concerns over the management of study patients. CRISIS 2, "Cyanokit Rescue in Smoke Inhalation Study," will assess the same clinical and laboratory evaluations as CRISIS 1; however, the enrolled patients will receive hydroxocobalamin therapy. This study is to be conducted in the postmarketing time period. The

results from the two studies will be used to evaluate the safety and efficacy of hydroxocobalamin in the setting of proposed use in a manner that allows comparison to a relevant control group.

## 8.8 Other Relevant Materials

The finding of efficacy for hydroxocobalamin relies primarily on a single controlled animal study and a single human study of safety, tolerability and pharmacokinetics conducted at one site. In addition, the clinical laboratory assessments were all performed at a single facility. Therefore, the Division of Scientific Investigations was asked to conduct a general investigation of each of the three sites to assure study conduct was as specified by the protocols and that due diligence was exercised at all sites for the handling and analyses of specimens. The findings of this investigation were pending at the time of this review.

In a review of the proposed product name, the Division of Medication Errors and Technical Support (DMETS) commented that Cyanokit is very similar to Cyanoject, which is injectable cyanocobalamin for the treatment of Vitamin B<sub>12</sub> deficiency. While it is not likely that the two products would be confused in the clinical setting, it is possible that a delay in treatment of cyanide poisoning, due to the release of the wrong product from the pharmacy, could result in unnecessary morbidity or mortality. Therefore, the Sponsor will be asked to reconsider the product name or provide a rationale that the proposed name will not affect safety.

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## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

The Sponsor has demonstrated that hydroxocobalamin confers a survival benefit over placebo in dogs when used to treat acute episodes of cyanide poisoning. A dosing effect for hydroxocobalamin was also demonstrated in the same study with an increased survival rate observed for the higher dose. The two doses evaluated in the dog study were determined to be equivalent to 5 and 10 grams for adult humans. Evidence was also provided suggesting that hydroxocobalamin confers a survival benefit in humans who were exposed to potentially lethal systemic levels of cyanide and treated with 5-10 g doses of hydroxocobalamin. Additional animal data indicated that the high blood levels of cyanocobalamin which result from the treatment of cyanide exposure do not incur significant risk.

In the safety and tolerability study, the Sponsor showed that the adverse effects of hydroxocobalamin tend to be dose related and, for the most part, well tolerated. The two most serious adverse events, hypertension and allergic reactions, can be readily monitored and treated. The occurrence of hypertension was not commonly seen in cyanide-toxic patients, who often presented in shock. Therefore, the occurrence of hypertension with the clinical use of hydroxocobalamin will likely be low, and may serve as an indicator that the diagnosis of cyanide poisoning should be reconsidered.

### **9.2 Recommendation on Regulatory Action**

It is recommended that an approval action be taken for this NDA.

Convincing evidence of efficacy and appropriate dosing was provided in the form of an adequate and well-controlled dog study and, to a lesser degree, uncontrolled human studies. The safety concerns identified in the human safety-tolerability-PK study are small compared to the risk of death from cyanide exposure; the risks are either well-tolerated, or can be readily identified by simple monitoring and easily treated should the need arise.

Cyanide poisoning may be rapid and lethal. The currently marketed antidotes are both kits containing sodium nitrite and amyl nitrite (both of which are unapproved drug products) and sodium thiosulfate (the only drug product approved as a cyanide antidote). The nitrite compounds produce a toxic intermediary, methemoglobin, which cannot be readily monitored and may have lethal consequences if the levels produced are in excess of that required to bind cyanide in the blood. Hydroxocobalamin presents two possible advantages over these kits with its lack of a toxic intermediary and lack of need to sequentially administer three different drug products.

### 9.3 Recommendation on Postmarketing Actions

The recommendations for postmarketing actions including PREA recommendations are contained in the Required Phase-4 Commitments section below.

#### 9.3.1 Risk Management Activity

The following are the recommendations of the Office of Surveillance and Epidemiology RiskMAP team:

1. The risks of hypertension and hypersensitivity associated with Cyanokit can be addressed with labeling and training, however the proposed labeling and training described in the RMP submission are not sufficient.
  - Labeling should inform health care providers on monitoring for and managing hypersensitivity reactions and hypertension (e.g., blood pressure should be monitored while Cyanokit is infusing and for a period of time following the infusion; the infusion should be stopped if the patient's blood pressure becomes dangerously elevated; the patient should be monitored for hypersensitivity reactions).
  - In addition to training healthcare practitioners on how to mix and infuse the product, we recommend training that focuses on monitoring for hypertension and hypersensitivity reactions and on interventions that may be required to manage these events. It is important that this training is incorporated into the roll-out of the product (rather than conducted after the product has been marketed for a period of time).
  - Because each healthcare practitioner trained would probably use Cyanokit only intermittently, over time healthcare practitioners could forget the messages relayed during Cyanokit training. Important messages on monitoring (including blood pressure monitoring and monitoring for hypersensitivity) and interventions should be included on the "quick use reference card" so that it is readily available to healthcare practitioners at the point of use.
2. Patient selection for administration of Cyanokit is not clear. Labeling and training should include guidance on who should receive Cyanokit. The "quick use reference card" should provide point-of-use guidance on patient selection.
3. The Sponsor does not list pharmacists among the healthcare practitioners that they plan to target for training. Pharmacists should be targeted for Cyanokit training (it is noted that pharmacists are responsible for the safe use of all medications within hospitals).
4. The RMP does not address the physical and chemical incompatibility between Cyanokit and a wide variety of other IV drugs which might be administered in an emergency setting (including sodium thiosulfate, another cyanide antidote), and with blood product transfusions. Cyanokit may be administered in a stressful and busy emergency setting or in the field where intravenous access is limited to a single intravenous line. Thus, the recommendations against concurrent administration with some drugs, which may necessitate a separate intravenous line, should be featured prominently on all labels,

labeling, and packaging to remind practitioners of these limitations. We recommend that a statement of these important incompatibilities be placed in the HIGHLIGHTS OF PRESCRIBING INFORMATION [e.g., Some drugs and blood products are not compatible with Cyanokit and should not be administered concurrently, thus administration of Cyanokit may necessitate a separate intravenous line (2.3).]

Additionally, information on incompatibilities and a list of compatible solutions should be included on the "quick use reference card" so that it is readily available to healthcare practitioners at the point of use. (Note: the labeling submission refers to an "instructions for use card" (7/5/06, attachment 5), rather than a "quick use reference card" but it appears these are the same item. This should be clarified).

5. The Sponsor proposes routine training on reconstitution and infusion of the product and routine pharmacovigilance as the management plan for Cyanokit. We do not feel that routine pharmacovigilance addresses the medication errors that might occur with the use of Cyanokit in the current package configuration. Specifically, we think training will not adequately address the potential for administration of half the usual dosage due to product design. We question why the kit contains two vials of 2.5 g hydroxocobalamin rather than a single vial containing the entire initial dose of 5 g. The directions describe administering 2.5 g in 100 mL of diluent over 7.5 minutes, which is then repeated to complete the initial dose of 5 g. Providing two vials to comprise one dose may be confusing to practitioners and may lead to dosing errors. Practitioners may assume that each vial comprises one dose resulting in half the recommended dose being administered. This drug may be used in a national disaster setting where multiple patients are triaged and treated concurrently. Practitioners may not remember that two vials comprise the initial dose of 5 g, or they may forget to infuse the second vial in such a hectic setting, increasing the risk of only one vial (2.5 g) being delivered. To decrease the potential for confusion, it seems practical to provide one 5 g vial, as the initial recommended dose is 5 g, diluted with 200 mL of diluent, which is administered over 15 minutes. Additionally, we recommend that the sponsor consider including the diluent within the Cyanokit packaging due to the incompatibility issues and also so that everything needed for mixing and administering Cyanokit is contained in the one package.
6. The RMP includes proposals for two Phase IV studies. CRISIS-II will be an observational study following up 50 patients treated with the Cyanokit following cyanide exposure from smoke inhalation, and we have no specific comments on that study. However, CRISIS-I is more problematic. This would be a study of 50 smoke inhalation victims from whom treatment with the Cyanokit is withheld. We do not see how such a study could be done ethically. We certainly would not allow a placebo-controlled study in this clinical setting, and the same objections would apply to an observational study of patients from whom treatment is withheld.

### 9.3.2 Required Phase 4 Commitments

The following Phase-4 Commitments should be required as a condition for approval.

1. To comply with the Animal Efficacy Rule, the Sponsor is required to gather safety and efficacy data when the product is used post-approval. To that end the Sponsor has

proposed two studies, CRISIS-1 and CRISIS-2. CRISIS-1 is an observational study to assess survival prior to approval of hydroxocobalamin. As the study is being conducted pre-approval, the ethical concerns raised by the OSE RiskMAP team do not apply; in addition, the study did not preclude any therapy which would normally be administered, including other cyanide antidotes. CRISIS-2 will be the vehicle by which the Sponsor obtains post-marketing safety and efficacy data. Protocols for both of these studies have been submitted for review by the Division. The Sponsor should commit to complete these trials and provide full study reports within three years of approval.

2. It is expected that hydroxocobalamin will be administered to pediatric patients. The Sponsor should commit to discussions with FDA to determine how best to provide suitable dosing information for this patient population. This commitment should be fulfilled within three years of approval.
3. Safety and efficacy data regarding the use of hydroxocobalamin in pediatric patients should be collected as part of CRISIS-1 and CRISIS-2. In addition, the Sponsor should commit to gather additional safety and efficacy data following the promulgation of dosing guidelines for this population. Essentially, this would entail repeating the CRISIS-2 study but only for pediatric patients. This commitment should be fulfilled within three years of approval of pediatric dosing guidelines, and should include a comparison with the safety and efficacy findings for the same population in the initial CRISIS-2 study.
4. The Sponsor should commit to the specification and qualification of the impurities described in the Pharmacology-Toxicology and CMC reviews within a year of approval.

### 9.3.3 Other Phase 4 Requests

No recommended Phase-4 requests are made.

## 9.4 Labeling Review

The following points are a summary of the major changes needed in the proposed labeling. A line-by-line review is included in the appendix.

1. The name Cyanokit refers to the contents of the package and not merely the hydroxocobalamin contained therein. Therefore, it should be relabeled to reflect that fact by specifying the contents of the package and removing the "2.5 g" which appears after the work Cyanokit."
2. The label should more clearly indicate that the starting dose is 5 g and that both vials of hydroxocobalamin must be administered to achieve that dose.
3. The label should more clearly indicate that the duration of the infusion is 7.5 minutes per vial and that the total starting dose of 5 g should be administered over 15 minutes. As packaged, it will be easy to confuse a single vial as the entire starting dose and infuse that over 15 minutes, which could limit efficacy.

4. The package should clearly indicate that diluent is not included. It should also indicate that a total of 200 mL is required for the dilution of the full starting dose – 100 mL per vial. The preferred use of normal saline as the diluent should be indicated.
5. The use of the word ' — ' in dosing should be eliminated as it implies pediatric dosing exists.
6. The elevation in blood pressure observed in the safety study should be described in the Warnings section.
7. In the Dosing and Administration section, the need for ~~————~~ blood pressure should be included along with a statement that elevations in blood pressure observed early in administration may be an indication that the patient is not suffering from cyanide toxicity and the diagnosis should be reconsidered.

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### **9.5 Comments to Applicant**

As the recommendation is for approval of this drug product, the only comments to be discussed with the Sponsor are those regarding labeling changes and the postmarketing commitments enumerated above.

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## **10 APPENDICES**

### **10.1 Review of Individual Study Reports**

#### **10.1.1 Study: EML 015722-H101**

“A double-blind, randomized, placebo-controlled, single-ascending-dose study, with a 4-week follow-up, of the safety, tolerability and pharmacokinetics of 4 intravenous doses (2.5g, 5g, 7.5g and 10g) of hydroxocobalamin in healthy subjects”

##### **10.1.1.1 Overall Design and Summary of Findings**

This study assessed the safety, tolerability and pharmacokinetics of four doses of hydroxocobalamin (OH-Co) administered to healthy adults. The study was conducted to fulfill the requirements set forth by the Division in meetings with the Sponsor during product development. In particular, the Division was concerned that patients may receive a cyanide antidote when they had not been exposed to cyanide or the cyanide exposure was nontoxic. In such instances, patients would have received a drug product from which they derived no benefit but were exposed to the attendant risks. Those risks were to be assessed. In addition, establishing the PK profile of hydroxocobalamin was considered an important component for establishing proper dosing intervals when cyanide exposure is prolonged (e.g., intestinal uptake following ingestion or transdermal absorption following skin exposure), or the exposure is to cyanogenic compounds (e.g., nitriles or sodium nitroprusside) whose metabolism results in prolonged release of cyanide.

##### **10.1.1.2 Study Plan**

This was a Phase-1 study in which four doses of hydroxocobalamin (OH-Co) were to be given to healthy adult volunteers. The doses included 2.5, 5, 7.5 and 10 g of hydroxocobalamin administered over 7.5, 15, 22 and 30 minutes, respectively.

For the safety assessments, the study drug was to be administered in a double-blind fashion to 200 subjects randomized in a 3:1 fashion for OH-Co and placebo, respectively. For the 2.5 and 7.5-g doses, 9 subjects were to receive OH-Co and 3 were to receive placebo; for the 5 and 10-g doses, 66 subjects were to receive OH-Co and 22 were to receive placebo.

For the PK assessments, 12 subjects (six males and six females) were to receive study drug for the 2.5 and 7.5-g doses. For each of these dose groups, 9 subjects were to receive OH-Co and three subjects were to receive placebo. The 5 and 10-g dose groups were to be assessed for PK only after the first eight subjects (six receiving OH-Co and two receiving placebo) were shown

to tolerate the doses as administered. A total of 16 subjects were to be assessed for PK profile in both the 5 and 10-g dose groups (12 receiving OH-Co and four receiving placebo). In addition, the first eight subjects enrolled in the 5 and 10-g dose groups were to have PK samples drawn at the end of the infusion and 10 minutes following the end of the infusion of the study drug to document tolerability.

#### **10.1.1.3 Objectives**

- To determine the safety and tolerability of four single-intravenous doses of free and total plasma cobalamins-(III) [ 2.5g over 7.5 minutes; 5g over 15 minutes; 7.5g over 22 minutes; and 10g over 30 minutes] compared to placebo
- To determine the pharmacokinetics (PK) of free and total plasma cobalamins-(III) in plasma and total cobalamins-(III) in urine in a subgroup of 12 subjects [9 on hydroxocobalamin (OH-Co) and three on placebo] each for the 2.5-g and the 7.5-g dose groups and 16 subjects (12 on OH-Co and 4 on placebo) each for the 5-g and 10-g dose groups.

#### **10.1.1.4 Design**

This study was designed as a single-center, double-blind, randomized, placebo-controlled, single-ascending dose study of the safety, tolerability and pharmacokinetics of four intravenous doses of hydroxocobalamin in healthy adult volunteers. The doses selected were based on those used in France, where the product is approved for use as an antidote to cyanide poisoning. These include an initial 5-g dose followed by a second 5-g dose if the initial dose does not produce a response.

As OH-Co was red in color, and it produces a reddish coloration of the skin and urine, blinding following initial dosing was expected to be limited; however, the study-drug container and intravenous tubing were to be opaque or covered to provide a degree of blinding during administration.

#### **10.1.1.5 Primary Efficacy Variable**

No efficacy assessments were made in this study.

#### **10.1.1.6 Secondary Efficacy Variables**

No efficacy assessments were made in this study.

#### **10.1.1.7 Population**