

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Cyanokit 2.5 g powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2.5 g of hydroxocobalamin. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Dark red crystalline powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of known or suspected cyanide poisoning.

Cyanokit is to be administered together with appropriate decontamination and supportive measures.

### 4.2 Posology and method of administration

#### Initial dose

Cyanokit is administered as an intravenous infusion over 15 minutes.

*Adults:* The initial dose of Cyanokit is 5 g.

*Paediatric patients:* In infants to adolescents, the initial dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

Body weight in kg	5	10	20	30	40	50	60
Initial dose in g	0.35	0.70	1.40	2.10	2.80	3.50	4.20
in ml	14	28	56	84	112	140	168

#### Subsequent dose

Depending upon the severity of the poisoning and the clinical response (see section 4.4), a second dose may be administered by intravenous infusion. The rate of infusion for the second dose ranges from 15 minutes (for patients extremely unstable) to 2 hours based on patient condition.

*Adults:* The subsequent dose of Cyanokit is 5 g.

*Paediatric patients:* In infants to adolescents, the subsequent dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

## Maximum dose

*Adults:* The maximum recommended dose is 10 g.

*Paediatric patients:* In infants to adolescents, the maximum recommended dose is 140 mg/kg not exceeding 10 g.

## Renal and hepatic impairments

Although the safety and efficacy of hydroxocobalamin have not been studied in renal and hepatic impairments, Cyanokit is administered as emergency therapy in an acute, life-threatening situation only and no dosage adjustment is required in these patients.

For instructions on preparation and handling, see section 6.6.

## **4.3 Contraindications**

None.

## **4.4 Special warnings and precautions for use**

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

Cyanokit does not substitute oxygen therapy and must not delay the set up of the above measures.

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

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

### Signs and symptoms of cyanide poisoning

Common signs and symptoms of cyanide poisoning include: nausea, vomiting, headache, altered mental status (e.g. confusion, disorientation), chest tightness, dyspnoea, tachypnoea or hyperpnoea (early), bradypnoea or apnoea (late), hypertension (early) or hypotension (late), cardiovascular collapse, seizures or coma, mydriasis, and plasma lactate concentration > 8 mmol/l.

In the setting of multiple casualties such as terrorism or chemical disaster, panic symptoms including tachypnoea and vomiting may mimic early cyanide poisoning signs. The presence of altered mental status (confusion and disorientation) and/or mydriasis is suggestive of true cyanide poisoning.

### Smoke inhalation

Not all smoke inhalation victims necessarily will have cyanide poisoning, but may present with burns, trauma, and exposure to additional toxic substances aggravating the clinical picture. Before Cyanokit is administered, it is recommended to check affected persons for the presence of the following:

- exposure to fire smoke in an enclosed area
- soot present around mouth, nose and/or oropharynx
- altered mental status

In this setting hypotension and/or a plasma lactate concentration  $\geq 10$  mmol/l (higher than the one mentioned under signs and symptoms due to the fact that carbon monoxide contributes to lactic

acidaemia) are highly suggestive of cyanide poisoning. In the presence of the above signs, treatment with Cyanokit must not be delayed to obtain a plasma lactate concentration.

### Hypersensitivity reactions

Known hypersensitivity to hydroxocobalamin or vitamin B<sub>12</sub> must be taken into benefit-risk consideration before administration of Cyanokit, since hypersensitive reactions may occur in patients receiving hydroxocobalamin (see section 4.8).

### Increase in blood pressure

Transient, generally asymptomatic, increase in blood pressure may occur in patients receiving hydroxocobalamin. The maximal increase in blood pressure has been observed toward the end of infusion.

### Effects on blood cyanide assay

Hydroxocobalamin will lower blood cyanide concentrations. While determination of blood cyanide concentration is not required and must not delay treatment with hydroxocobalamin, it may be useful for documenting cyanide poisoning. If a cyanide blood level determination is planned, it is recommended to draw the blood sample before initiation of treatment with Cyanokit.

### Interference with burn assessment

Because of its deep red colour, hydroxocobalamin has the potential to induce a red colouration of the skin and therefore may interfere with burn assessment. However, skin lesions, oedema, and pain are highly suggestive of burns.

### Interference with laboratory tests

Because of its deep red colour, hydroxocobalamin has the potential to interfere with determination of laboratory parameters (e.g. clinical chemistry, haematology, coagulation, and urine parameters). *In vitro* tests indicate that the extent and duration of the interference is dependant on numerous factors such as the dose of hydroxocobalamin, analyte, analyte concentration, methodology, analyser, concentrations of cobalamins-(III) including cyanocobalamin and partially the time between sampling and measurement.

Based on *in vitro* studies and pharmacokinetic data obtained in healthy volunteers the following table describes interference with laboratory tests that may be observed following a 5 g dose of hydroxocobalamin. Interference following a 10 g dose can be expected to last up to an additional 24 hours. The extent and duration of interference in cyanide-poisoned patients may differ according to the severity of intoxication. Results may vary considerably from one analyser to another, therefore, caution is required when reporting and interpreting laboratory results.

### **Observed *in vitro* interferences of hydroxocobalamin with laboratory tests**

Laboratory parameter	No interference observed	Artificially increased*	Artificially decreased*	Unpredictable***	Duration of interference after a 5 g dose
Clinical chemistry	Calcium Sodium Potassium Chloride Urea Gamma glutamyl transferase (GGT)	Creatinine Total and conjugate bilirubin** Triglycerides Cholesterol Total protein Glucose Albumin Alkaline	Alanine aminotransferase (ALT) Amylase	Phosphate Uric acid Aspartate aminotransferase (AST) Creatine kinase (CK) Creatinine kinase isoenzym MB (CKMB) Lactate dehydrogenase	24 hours with the exception of bilirubin (up to 4 days)

Laboratory parameter	No interference observed	Artificially increased*	Artificially decreased*	Unpredictable***	Duration of interference after a 5 g dose
		phosphatase		(LDH)	
Haematology	Erythrocytes Haematocrit Mean corpuscular volume (MCV) Leucocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets	Haemoglobin (Hb) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC)			12-16 hours
Coagulation				Activated partial thromboplastin time (aPTT) Prothrombin time (PT) Quick or INR	24 hours

\*  $\geq 10\%$  interference observed on at least one analyser

\*\* Artificially decreased using the diazo method

\*\*\* Inconsistent results

Analysers used: ACL Futura (Instrumentation Laboratory), AxSYM/Architect (Abbott), BM Coasys<sup>110</sup> (Boehringer Mannheim), CellDyn 3700 (Abbott), Clinitek 500 (Bayer), Cobas Integra 700, 400 (Roche), Gen-S Coultronics, Hitachi 917, STA<sup>®</sup> Compact, Vitros 950 (Ortho Diagnostics)

Hydroxocobalamin may interfere with all urine colorimetric parameters. The effects on these tests typically last 48 hours after a 5 g dose, but may persist for longer periods. Caution is required in the interpretation of urinary colorimetric tests for as long as chromaturia is present.

#### Use with other cyanide antidotes

The safety of administering other cyanide antidotes simultaneously with Cyanokit has not been established (see section 6.2). If the decision is made to administer another cyanide antidote with Cyanokit, these medicinal products must not be administered concurrently in the same intravenous line (see section 6.2).

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

#### **4.6 Pregnancy and lactation**

For hydroxocobalamin, no clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). However, due to the potentially life-threatening condition and the lack of suitable alternative treatments, hydroxocobalamin can be administered during pregnancy.

Hydroxocobalamin may be excreted in human milk. Because hydroxocobalamin will be administered in potentially life-threatening situations, breast-feeding is not a contraindication to its use.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive or to use machines have been performed.

## 4.8 Undesirable effects

A total of 347 subjects were exposed to hydroxocobalamin in clinical studies. Of these 347 subjects, 245 patients had suspected exposure to cyanide at the time of hydroxocobalamin administration. The remaining 102 subjects were healthy volunteers who had not been exposed to cyanide at the time of hydroxocobalamin administration.

Most patients will experience a reversible red colouration of the skin and mucous membranes that may last up to 15 days after administration of Cyanokit. All patients will show a dark red colouration of the urine quite marked during the three days following administration. Urine colouration may last up to 35 days after administration of Cyanokit.

The following undesirable effects have been reported in association with Cyanokit use. However, because of the limitations of the available data, it is not possible to apply frequency estimations:

### Investigations

Cyanokit may cause red discolouration of the plasma, which may cause artificial elevation or reduction in the levels of certain laboratory parameters (see section 4.5).

### Cardiac disorders

Ventricular extrasystoles. An increase in heart rate was observed in cyanide-poisoned patients.

### Blood and lymphatic system disorders

Decrease in the percentage of lymphocytes.

### Nervous system disorders

Memory impairment; dizziness.

### Eye disorders

Swelling, irritation, redness.

### Respiratory, thoracic and mediastinal disorders

Pleural effusion, dyspnoea, throat tightness, dry throat, chest discomfort.

### Gastrointestinal disorders

Abdominal discomfort, dyspepsia, diarrhoea, vomiting, nausea, dysphagia.

### Renal and urinary disorders

Chromaturia (see above).

### Skin and subcutaneous tissue disorders

Reversible red colouration of the skin and mucous membranes (see above). Pustular rashes, which may last for several weeks, affecting mainly the face and the neck.

### Vascular disorders

Transient increase in blood pressure, usually resolving within several hours; hot flush. A decrease in blood pressure was observed in cyanide-poisoned patients.

### General disorders and administration site conditions

Headache; injection site reaction; peripheral oedema.

### Immune system disorders

Allergic reactions including angioneurotic oedema, skin eruption, urticaria and pruritus.

### Psychiatric disorders

Restlessness.

## **4.9 Overdose**

Doses as high as 15 g have been administered without reported specific dose related adverse reactions. If overdose occurs, treatment is directed to the management of symptoms. Haemodialysis may be effective in such a circumstance, but is only indicated in the event of significant hydroxocobalamin-related toxicity.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antidote, ATC code: V03AB33

#### Mechanism of action

The action of hydroxocobalamin in the treatment of cyanide poisoning is based on its ability to tightly bind cyanide ions. Each hydroxocobalamin molecule can bind one cyanide ion by substituting the hydroxo ligand linked to the trivalent cobalt ion to form cyanocobalamin. Cyanocobalamin is a stable, non-toxic compound that is excreted in the urine.

#### Efficacy

Due to ethical considerations, no controlled human efficacy studies have been performed.

- Animal pharmacology

The effectiveness of hydroxocobalamin was examined in a controlled study in cyanide-poisoned adult dogs. Dogs were poisoned by intravenous administration of a lethal dose of potassium cyanide. Dogs then received sodium chloride 9 mg/ml, 75 mg/kg or 150 mg/kg hydroxocobalamin, administered intravenously over 7.5 minutes. The 75 mg/kg and 150 mg/kg doses are approximately equivalent to 5 g and 10 g of hydroxocobalamin, respectively, in humans, not only on a body weight basis but also on  $C_{max}$  basis of hydroxocobalamin [total cobalamins-(III), see section 5.2].

Survival at hour 4 and at day 14 was significantly greater in 75 mg/kg and 150 mg/kg hydroxocobalamin dose groups compared with dogs receiving sodium chloride 9 mg/ml alone:

## Survival of cyanide-poisoned dogs

Parameter	Treatment		
	Sodium chloride 9 mg/ml (N=17)	Hydroxocobalamin	
		75 mg/kg (N=19)	150 mg/kg (N=18)
Survival at Hour 4, N (%)	7 (41)	18 (95)*	18 (100)*
Survival at Day 14, N (%)	3 (18)	15 (79)*	18 (100)*

\* p<0.025

Histopathology revealed brain lesions that were consistent with cyanide-induced hypoxia. The incidence of brain lesions was markedly lower in dogs having received 150 mg/kg hydroxocobalamin than in dogs having received 75 mg/kg hydroxocobalamin or sodium chloride 9 mg/ml.

The rapid and complete recovery of haemodynamics and subsequently of blood gases, pH, and lactate after cyanide poisoning likely contributed to the better outcome of the hydroxocobalamin-treated animals. Hydroxocobalamin reduced whole blood cyanide concentrations from about 120 nmol/ml to 30-40 nmol/ml by the end of the infusion compared with 70 nmol/ml in dogs receiving sodium chloride 9 mg/ml alone.

- Cyanide-poisoned patients

A total of 245 patients with suspected or known cyanide-poisoning were included in the clinical studies of the efficacy of hydroxocobalamin as an antidote. Of the 213 patients in whom the outcome was known the survival was 58%. Of the 89 patients who died, 63 were initially found in cardiac arrest, suggesting that many of these patients had almost certainly suffered irreparable brain injury prior to administration of hydroxocobalamin. Among 144 patients not in initial cardiac arrest whose outcomes were known, 118 (82%) survived. Furthermore, in 34 patients with known cyanide concentrations above the lethal threshold ( $\geq 100 \mu\text{mol/l}$ ), 21 (62%) survived following treatment with hydroxocobalamin.

Administration of hydroxocobalamin was generally associated with a normalisation of blood pressure (systolic blood pressure  $> 90 \text{ mmHg}$ ) in 17 of 21 patients (81%) who had low blood pressure (systolic blood pressure  $> 0$  and  $\leq 90 \text{ mmHg}$ ) after exposure to cyanide. Where neurological assessment over time was possible, (96 patients of the 171 patients who presented with neurological symptoms prior to hydroxocobalamin administration), 51 (53%) patients receiving hydroxocobalamin showed improvement or a complete restoration.

- Elderly

Approximately 50 known or suspected cyanide victims aged 65 or older received hydroxocobalamin in clinical studies. In general, the effectiveness of hydroxocobalamin in these patients was similar to that of younger patients.

- Paediatric patients

Documentation on efficacy is available for 54 paediatric patients. The mean age of the paediatric patients was about six years and the mean dose of hydroxocobalamin was about 120 mg/kg body weight. The survival rate of 41% depended very much on the clinical situation. Out of the 20 paediatric patients without initial cardiac arrest, 18 (90%) survived, of whom 4 with sequelae. In general, the effectiveness of hydroxocobalamin in paediatric patients was similar to that of adults.

## 5.2 Pharmacokinetic properties

Following intravenous administration of Cyanokit, significant binding to plasma proteins and low molecular weight physiological compounds occurs, to form various cobalamin-(III) complexes by replacing the hydroxo ligand. The low molecular weight cobalamins-(III) formed including



hydroxocobalamin are termed free cobalamins-(III); the sum of free and protein-bound cobalamins is termed total cobalamins-(III). In order to reflect the exposure to the sum of all derivatives, pharmacokinetics of cobalamins-(III) were investigated instead of hydroxocobalamin, requiring the concentration unit  $\mu\text{g eq/ml}$  (i.e. cobalamin-(III) entity without specific ligand).

Dose-proportional pharmacokinetics were observed following single dose intravenous administration of 2.5 to 10 g of Cyanokit in healthy volunteers. Mean free and total cobalamins-(III)  $C_{\text{max}}$  values of 113 and 579  $\mu\text{g eq/ml}$ , respectively, were determined following a dose of 5 g Cyanokit (the recommended initial dose). Similarly, mean free and total cobalamins-(III)  $C_{\text{max}}$  values of 197 and 995  $\mu\text{g eq/ml}$ , respectively, were determined following the dose of 10 g Cyanokit. The predominant mean half-life of free and total cobalamins-(III) was approximately 26 to 31 hours at the 5 and 10 g dose level.

The mean total amount of cobalamins-(III) excreted in urine during the collection period of 72 hours was approximately 60% of a 5 g dose and approximately 50% of a 10 g dose of Cyanokit. Overall, the total urinary excretion was calculated to be at least 60 to 70% of the administered dose. The majority of the urinary excretion occurred during the first 24 hours, but red coloured urine was observed for up to 35 days following the intravenous infusion.

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

In cyanide-poisoned patients, hydroxocobalamin is expected to bind cyanide to form cyanocobalamin, which is excreted in the urine. The pharmacokinetics of total cobalamins-(III) in this population may be affected by the body's cyanide load, since cyanocobalamin was reported to exhibit a 2-3 times lower half-life than total cobalamins-(III) in healthy volunteers.

### **5.3 Preclinical safety data**

In anaesthetised rabbits, hydroxocobalamin exerted haemodynamic effects (increased mean arterial blood pressure and total peripheral resistance, decreased cardiac output) related to its nitric oxide-scavenging property.

No special hazard for humans was identified based on conventional studies of single and repeated dose toxicity and genotoxicity. The liver and kidney were found to be the major target organs. However findings were only seen at exposure levels considered being higher than the maximum human exposure, indicating limited relevance to clinical use. In particular, liver fibrosis was observed in dogs after administration of hydroxocobalamin for 4 weeks at 300 mg/kg. The relevance of this finding to humans is unlikely since it was not reported in short-term studies conducted with hydroxocobalamin.

Only limited data on embryo-fetal development are available which do not allow an assessment on the impact of high intravenous dose levels of hydroxocobalamin on embryo-fetal development. No data are available on male and female fertility as well as on peri- and postnatal development. Hydroxocobalamin has not been evaluated for carcinogenic potential.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Hydrochloric acid

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Physical incompatibility (particle formation) was observed with the mixture of hydroxocobalamin in solution and the following medicinal products: diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, pentobarbital, phenytoin sodium, propofol and thiopental. Chemical incompatibility was observed with sodium thiosulfate, sodium nitrite, and has been reported with ascorbic acid. Consequently, these medicinal products must not be administered simultaneously through the same intravenous line as hydroxocobalamin.

Simultaneous administration of hydroxocobalamin and blood products (whole blood, packed red cells, platelet concentrate and fresh frozen plasma) through the same intravenous line is not recommended (see section 6.6).

### **6.3 Shelf life**

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 6 hours at a temperature between 2°C and 40°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 2°C to 8°C.

### **6.4 Special precautions for storage**

Do not store above 25°C.

For the purpose of ambulatory use, Cyanokit may be exposed during short periods to the temperature variations of usual transport (15 days submitted to temperatures ranging from 5°C to 40°C), transport in the desert (4 days submitted to temperatures ranging from 5°C to 60°C) and freezing/defrosting cycles (15 days submitted to temperatures ranging from -20°C to 40°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

Type II colourless 250 ml glass vial closed with bromobutyl rubber stopper and an aluminium cap with a plastic lid. Each vial contains 2.5 g powder for solution for infusion.

Each carton contains two glass vials (each glass vial packed in one cardboard box), two sterile transfer devices, one sterile intravenous infusion set and one sterile short catheter for administration to children.

### **6.6 Special precautions for disposal and other handling**

Each vial is to be reconstituted with 100 ml of diluent using the supplied sterile transfer device. Sodium chloride 9 mg/ml (0.9%) solution for injection is the recommended diluent. Only when sodium chloride 9 mg/ml (0.9%) solution for injection is not available, Lactated Ringer solution or 5% glucose can also be used.

The Cyanokit vial is to be rocked or inverted for at least 30 seconds to mix the solution. It must not be shaken as shaking the vial may cause foam and therefore may make checking reconstitution less easy. Because the reconstituted solution is a dark red solution, some insoluble particles may not be seen. The intravenous infusion set provided in the kit must then be used as it includes an appropriate filter and is to be primed with the reconstituted solution. Repeat this procedure if necessary with the second vial.

If blood products (whole blood, packed red cells, platelet concentrate and fresh frozen plasma) and hydroxocobalamin are administered simultaneously, use of separate intravenous lines (preferably on contralateral extremities) is recommended (see section 6.2).

**7. MARKETING AUTHORISATION HOLDER**

Merck Santé s.a.s.  
37, rue Saint-Romain  
69379 Lyon Cedex 08  
France

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

**ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER  
RESPONSIBLE FOR BATCH RELEASE**
  
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Merck Santé s.a.s.  
Centre de production de Semoy  
2, rue du Pressoir Vert  
FR-45400 Semoy  
France

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

• **OTHER CONDITIONS**

*Pharmacovigilance system*

The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

*Risk Management Plan*

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Cyanokit 2.5 g powder for solution for infusion  
Hydroxocobalamin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 2.5 g of hydroxocobalamin. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.

**3. LIST OF EXCIPIENTS**

Excipient: Hydrochloric acid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Two vials, each containing 2.5 g of powder for solution for infusion.  
Two transfer devices.  
One intravenous infusion set.  
One short catheter for administration to children.

This kit does not contain diluent.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP



**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

Read the leaflet for storage conditions in ambulatory use.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Santé s.a.s.  
37, rue Saint-Romain  
69379 Lyon Cedex 08  
France

**12. MARKETING AUTHORISATION NUMBER(S)****13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARDBOARD BOX**

**1. NAME OF THE MEDICINAL PRODUCT**

Cyanokit 2.5 g powder for solution for infusion  
Hydroxocobalamin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 2.5 g of hydroxocobalamin. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.

**3. LIST OF EXCIPIENTS**

Excipient: Hydrochloric acid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

One vial containing 2.5 g of powder for solution for infusion.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Santé s.a.s.  
37, rue Saint-Romain  
69379 Lyon Cedex 08  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL**

**1. NAME OF THE MEDICINAL PRODUCT**

Cyanokit 2.5 g powder for solution for infusion  
Hydroxocobalamin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 2.5 g of hydroxocobalamin. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.

**3. LIST OF EXCIPIENTS**

Excipient: Hydrochloric acid.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion containing 2.5 g of hydroxocobalamin.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Santé s.a.s.  
37, rue Saint-Romain  
69379 Lyon Cedex 08  
France

**12. MARKETING AUTHORISATION NUMBER(S)**

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**MEDICAL OR HEALTHCARE PROFESSIONALS EDUCATIONAL STICKER**

“To be attached to the patient’s medical record:

Cyanokit has been administered to this patient.

Cyanokit may interfere with burn assessment (red coloration of the skin) and laboratory tests (see SPC).”

**B. PACKAGE LEAFLET**

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **Cyanokit 2.5 g powder for solution for infusion** hydroxocobalamin

**Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Cyanokit is and what it is used for
2. Before you use Cyanokit
3. How to use Cyanokit
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## **1. WHAT CYANOKIT IS AND WHAT IT IS USED FOR**

Cyanokit is an antidote for the treatment of known or suspected cyanide poisoning. Cyanokit is to be administered together with appropriate decontamination and supportive measures.

Cyanide is a highly poisonous chemical. Cyanide poisoning may be caused by exposure to smoke from household and industrial fires, breathing or swallowing cyanide, or contact with cyanide on skin.

## **2. BEFORE YOU USE CYANOKIT**

### **Take special care with Cyanokit**

Tell your doctor or other health personnel

- if you are allergic to hydroxocobalamin or vitamin B<sub>12</sub>. They will have to take it into account before treating you with Cyanokit.
- that you have been treated with Cyanokit if you need to have any blood or urine tests. Cyanokit may modify the results of these tests.

### **Using other medicines**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Detailed information for your doctor or other health personnel regarding simultaneous administration of Cyanokit with other medicines can be found at the end of this package leaflet (see 'Handling instructions').

### **Pregnancy and breast-feeding**

This medicine is an emergency treatment. It can be administered during pregnancy and breast-feeding.



## **Driving and using machines**

It is not known whether Cyanokit affects the ability to drive or use machines.

## **3. HOW TO USE CYANOKIT**

You will have Cyanokit by infusion into a vein. You may have one or two infusions.

You will have the first infusion of Cyanokit over 15 minutes. If you need a second infusion, you will have it over 15 minutes to 2 hours. It depends on how serious the poisoning is.

Detailed instructions for your doctor or other health personnel on how to prepare the Cyanokit infusion and how to determine the dose can be found at the end of this package leaflet (see 'Handling instructions').

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Cyanokit can cause side effects, although not everybody gets them. The following side effects may be expected:

Most patients will experience a reversible red colouration of the skin and membranes lining body cavities (mucous membranes) that may last up to 15 days after administration of Cyanokit. All patients will show a dark red colouration of the urine quite marked during the three days following administration. Urine colouration may last up to 35 days after administration of Cyanokit.

### Allergy (hypersensitivity)

Tell your doctor **immediately** if you have the following symptoms during or after this treatment:

- swelling around the eyes, lips, tongue, throat or hands
- breathing difficulties, hoarseness, difficulty in speaking
- skin redness, nettle rash (urticaria) or itching.

**Such side effects may be serious and need immediate attention.**

### Heart and blood pressure problems

- symptoms such as headache or dizziness, as they may be due to a rise in blood pressure. This rise in blood pressure especially occurs at the end of having this treatment and usually settles down within several hours
- irregular heart beat
- redness of the face (flush).

A decrease in blood pressure and a faster heart beat have also been observed in patients who have cyanide poisoning.

### Breathing and chest problems

- fluid in the chest (pleural effusion)
- breathing difficulties
- a feeling of tightness in the throat
- dry throat
- chest discomfort.

### Gastrointestinal (digestive) problems

- discomfort in your stomach
- indigestion
- diarrhoea
- feeling sick (nausea)
- being sick (vomiting)
- difficulty in swallowing.

#### Eye problems

- swelling, irritation, redness.

#### Skin reactions

- blister-like lesions on the skin (pustular rashes). These may last for several weeks, and affect mainly the face and the neck.
- inflammation in the part of the body where the medicine was infused.

#### Other side effects

- restlessness
- problems with memory
- dizziness
- headache
- swelling of ankles
- changes in the results of blood tests for certain white blood cells (lymphocytes)
- coloured plasma, which may cause artificial elevation or reduction in the levels of certain laboratory parameters.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## **5. HOW TO STORE CYANOKIT**

Keep out of the reach and sight of children.

Do not use Cyanokit after the expiry date which is stated on the vial, the cardboard box and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

For the purpose of ambulatory use, Cyanokit may be exposed during short periods to the temperature variations of

- usual transport (15 days submitted to temperatures ranging from 5 to 40°C)
- transport in the desert (4 days submitted to temperatures ranging from 5 to 60°C) and
- freezing/defrosting cycles (15 days submitted to temperatures ranging from -20 to 40°C).

For storage conditions of the reconstituted medicine, see 'Handling instructions' at the end of this package leaflet.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Cyanokit contains

- The active substance is hydroxocobalamin. Each vial contains 2.5 g of powder for solution for infusion. After reconstitution with 100 ml of diluent, each ml of the reconstituted solution contains 25 mg of hydroxocobalamin.
- The other ingredient is hydrochloric acid.

### What Cyanokit looks like and contents of the pack

Cyanokit powder for solution for infusion is a dark red crystalline powder supplied in a glass vial closed with bromobutyl rubber stopper and an aluminium cap with a plastic lid.

Each carton contains two glass vials (each glass vial packed in one cardboard box), two sterile transfer devices, one sterile intravenous infusion set and one sterile short catheter for administration to children.

### Marketing Authorisation Holder

Merck Santé s.a.s.  
37, rue Saint-Romain  
69379 Lyon Cedex 08  
France

### Manufacturer

Merck Santé s.a.s. / SEMOY  
2, rue du Pressoir Vert  
45400 Semoy  
France

### This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu/>.

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The following information is intended for medical or healthcare professionals only:

### Handling Instructions

**Treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of seizures. Consideration must be given to decontamination measures based on the route of exposure.**

**Cyanokit does not substitute oxygen therapy and must not delay the set up of the above measures.**

**The presence and extent of cyanide poisoning are often initially unknown. There is no widely available, rapid, confirmatory cyanide blood test. However, if a cyanide blood level determination is planned, it is recommended to draw the blood sample before initiation of treatment with Cyanokit. Treatment decisions must be made on the basis of clinical history**

**and/or signs and symptoms of cyanide intoxication. If there is clinical suspicion of cyanide poisoning, it is strongly recommended that Cyanokit be administered without delay.**

### **Preparation of Cyanokit**

Each vial is to be reconstituted **with 100 ml of diluent** using the supplied sterile transfer device. **Sodium chloride 9 mg/ml (0.9%) solution for injection** is the recommended diluent. Only when sodium chloride 9 mg/ml (0.9%) solution for injection is not available, Lactated Ringer solution or 5% glucose can also be used.

The Cyanokit vial is to be rocked or inverted for at least 30 seconds to mix the solution. It must not be shaken as shaking the vial may cause foam and therefore may make checking reconstitution less easy. Because the reconstituted solution is a dark red solution, some insoluble particles may not be seen. The intravenous infusion set provided in the kit must then be used as it includes an appropriate filter and is to be primed with the reconstituted solution. Repeat this procedure if necessary with the second vial.

### **Initial dose**

Cyanokit is administered as an intravenous infusion over 15 minutes.

*Adults:* The initial dose of Cyanokit is 5 g.

*Paediatric patients:* In infants to adolescents, the initial dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

Body weight in kg	5	10	20	30	40	50	60
Initial dose in g	0.35	0.70	1.40	2.10	2.80	3.50	4.20
in ml	14	28	56	84	112	140	168

### **Subsequent dose**

Depending upon the severity of the poisoning and the clinical response, a second dose may be administered by intravenous infusion. The rate of infusion for the second dose ranges from 15 minutes (for patients extremely unstable) to 2 hours based on patient condition.

*Adults:* The subsequent dose of Cyanokit is 5 g.

*Paediatric patients:* In infants to adolescents, the subsequent dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

### **Maximum dose**

*Adults:* The maximum recommended dose is 10 g.

*Paediatric patients:* In infants to adolescents, the maximum recommended dose is 140 mg/kg not exceeding 10 g.

### **Renal and hepatic impairments**

No dosage adjustment is required in these patients.

### **Simultaneous administration of Cyanokit and other products**

Cyanokit must not be mixed with other medicinal products except sodium chloride 9 mg/ml (0.9%) solution for injection or Lactated Ringer solution or 5% glucose.

If blood products (whole blood, packed red cells, platelet concentrate and fresh frozen plasma) and hydroxocobalamin are administered simultaneously, use of separate intravenous lines (preferably on contralateral extremities) is recommended.

**Combination with another cyanide antidote:** Chemical incompatibility was observed with sodium thiosulfate and sodium nitrite. If the decision is made to administer another cyanide antidote with Cyanokit, these medicinal products must not be administered concurrently in the same intravenous line.

### **In-use stability of the reconstituted solution**

Chemical and physical in-use stability has been demonstrated for 6 hours at a temperature between 2°C to 40°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at 2°C to 8°C.