Cyanokit

1. NAME OF THE MEDICINAL PRODUCT

Cyanokit 5 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The vial contains 5 g of hydroxocobalamin.
After reconstitution with 200 mL of diluent, each mL of the reconstituted solution contains 25 mg of hydroxocobalamin.

For the 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 in all age ranges.

Cyanokit is to be administered together with appropriate decontamination and supportive measures (see section 4.4).

4.2 Posology and method of administration

Posology

Initial dose
Adults: The initial dose of Cyanokit is 5 g (200 mL, complete volume of reconstituted solution).

Paediatric population: In infants to adolescents (0 to 18 years old), 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.

Adults: The subsequent dose of Cyanokit is 5 g (200 mL, complete volume of reconstituted solution).

Paediatric population: In infants to adolescents (0 to 18 years old), the subsequent dose of Cyanokit is 70 mg/kg body weight not exceeding 5 g.

Maximum dose
Adults: The maximum total recommended dose is 10 g.

Paediatric population: In infants to adolescents (0 to 18 years old), the maximum total recommended dose is 140 mg/kg not exceeding 10 g.

Renal and hepatic impairment
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 dose adjustment is required in these patients.

Method of administration
Initial dose of Cyanokit is administered as an intravenous infusion over 15 minutes.

The rate of intravenous infusion for the second dose ranges from 15 minutes (for patients extremely unstable) to 2 hours based on patient condition.

For instructions on reconstitution of the medicinal product before administration, 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 ≥ 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_{12} must be taken into benefit-risk consideration before administration of Cyanokit, since hypersensitive reactions may occur in patients receiving hydroxocobalamin (see section 4.8).

Renal disorders
Oxalate crystals have been observed in the urine of healthy volunteers given hydroxocobalamin. Cases of acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals present have been reported in patients treated with hydroxocobalamin following known or suspected cyanide poisoning. In some situations, hemodialysis was required to achieve recovery (see section 4.8).

Therefore, as a precaution, after Cyanokit administration, regular monitoring of renal function (including blood urea nitrogen and serum creatinine) should be performed until 7 days after drug onset.

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 (see section 4.8).

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 phosphatase	Alanine aminotransferase (ALT) Amylase	Phosphate Uric acid Aspartate aminotransferase (AST) Creatine kinase (CK) Creatine kinase isoenzym MB (CKMB) Lactate dehydrogenase (LDH)	24 hours with the exception of bilirubin (up to 4 days)
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

* ≥ 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 Coasys110 (Boehringer Mannheim), CellDyn 3700 (Abbott), Clinitek 500 (Bayer), Cobas Integra 700, 400 (Roche), Gen-S Coultronics, Hitachi 917, STA® Compact, Vitros 950 (Ortho Diagnostics)

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.

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

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 Fertility, pregnancy and lactation
Pregnancy
Animal studies have shown teratogenic effects following daily exposure throughout organogenesis (see section 5.3). There are no adequate data from the use of hydroxocobalamin in pregnant women and the potential risk for humans is unknown.

However, taken into account:
- that no more than two injections of hydroxocobalamin are to be administered,
- the potentially life threatening condition,
- the lack of alternative treatment,
- hydroxocobalamin may be given to a pregnant woman.

In case of known pregnancy at the time of treatment with Cyanokit or in case that pregnancy becomes known after treatment with Cyanokit, health care professionals are requested to promptly report the exposure during pregnancy to the Marketing Authorisation Holder and/or Health Authorities and to carefully follow-up on the pregnancy and its outcome.

Breast-feeding
Because hydroxocobalamin will be administered in potentially life-threatening situations, breast-feeding is not a contraindication to its use. In the absence of data in breast-fed infants, breast-feeding discontinuation is recommended after receiving Cyanokit.

Fertility
No studies on fertility have been performed (see section 5.3).

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Summary of the safety profile
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.

List of adverse reactions
The following adverse reactions 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:

Blood and lymphatic system disorders
Decrease in the percentage of lymphocytes.

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

Psychiatric disorders
Restlessness.

Nervous system disorders
Memory impairment; dizziness.

Eye disorders
Swelling, irritation, redness.

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

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.

Respiratory, thoracic and mediastinal disorders
Pleural effusion, dyspnoea, throat tightness, dry throat, chest discomfort.

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

Skin and subcutaneous tissue disorders
Reversible red colouration of the skin and mucous membranes: most patients will experience it up to 15 days after administration of Cyanokit.

Pustular rashes, which may last for several weeks, affecting mainly the face and the neck.

Renal and urinary disorders
- Acute renal failure with acute tubular necrosis, renal impairment, urine calcium oxalate crystals present (see section 4.4).
- Chromaturia: all patients will show a dark red colouration of the urine quite marked during the first three days following administration. Urine colouration may last up to 35 days after administration of Cyanokit (see section 4.4).

General disorders and administration site conditions
Headache; injection site reaction; peripheral oedema.

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 4.4).

Paediatric population
Limited data on children (0 to 18 years old) treated with hydroxocobalamin did not show any difference in the safety profile of hydroxocobalamin between adults and children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, website: www.bfarm.de.

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. However, hydroxocobalamin because of its deep red colour may interfere with the performance of haemodialysis machines (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antidotes
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 (≥ 100 µmol/L), 21 (62%) survived following treatment with hydroxocobalamin.

Administration of hydroxocobalamin was generally associated with a normalisation of blood pressure (systolic blood pressure > 90 mmHg) in 17 of 21 patients (81%) who had low blood pressure (systolic blood pressure > 0 and ≤ 90 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 population

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, phar-

macokinetics of cobalamins-(III) were investigated instead of hydroxocobalamin, requiring the concentration unit µg 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_{max} values of 113 and 579 µg eq/mL, respectively, were determined following a dose of 5 g Cyanokit (the recommended initial dose). Similarly, mean free and total cobalamins-(III) C_{max} values of 197 and 995 µg eq/mL, respectively, were determined following the dose of 10 g 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.

Developmental toxicity, including teratogenicity, was observed in rats and rabbits at dose levels of 150 mg/kg and higher administered daily throughout organogenesis. The dose of 150 mg/kg approximately corresponds to the maximum recommended human dose.

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 (for pH-adjustment)

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 reconstituted solution and the following medicinal products: diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, pentobarbital, phenytoin sodium, propofol and thiopental.

Chemical incompatibility was observed with the mixture of hydroxocobalamin reconstituted solution and the following medicinal products: epinephrine, lidocaine hydrochloride, adenosine, atropine, midazolam, ketamin, succinylcholine chloride, amiodarone hydrochloride, sodium bicarbonate, sodium thiosulfate, sodium nitrite, and has been reported with ascorbic acid.

Consequently, these and other 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.

6.3 Shelf life

3 years.

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). If these temporary conditions have been exceeded, the product should be discarded.

Chemical and physical in-use stability of the reconstituted solution with sodium chloride 9 mg/mL (0.9%) has been demonstrated for 6 hours at a temperature between 2 °C and 40 °C. From a microbiological point of view, the medicinal 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 ºC..

6.4 Special precautions for storage

Do not store above 25°C!

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

6.5 Nature and contents of container

Type I colourless 250 mL glass vial closed with bromobutyl rubber stopper and an aluminium cap with a plastic lid.

Each pack contains one vial packed in one cardboard box, one sterile transfer device, one sterile intravenous infusion set and one sterile short catheter for administration to children.

6.6 Special precautions for disposal amd other handling

No special requirements for disposal.

The vial is to be reconstituted with 200 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 glucose 50 mg/mL (5%) solution for injection can also be used.
The Cyanokit vial is to be rocked or inverted for at least 1 minute 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.

7. MARKETING AUTHORISATION HOLDER

SERB S.A.
Avenue Louise 480
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/420/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 November 2007
Date of latest renewal: 20 July 2012

10. DATE OF REVISION OF THE TEXT

07.2017

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