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Importation of European (EU)-labelled Cyanokit (Hydroxocobalamin) 5 g/vial powder for infusion due to the shortage of Canadian-authorized Cyanokit

January 24, 2025

Dear Healthcare Provider,

There is a critical shortage of Cyanokit (Hydroxocobalamin) 5 g/vial powder for infusion in Canada. The reason of the shortage of the Canadian-authorized Cyanokit is related to a potential risk of microbial contamination of certain batches, which paused the production. It has to be highlighted that the EU-labelled Cyanokit product could also be potentially impacted by the same issue. Please refer to additional information provided under **Safety and security of Canadian and EU-labelled Cyanokit**.

Given the medical necessity of this product and to help mitigate the shortage, Health Canada has permitted the exceptional, temporary importation and sale of EU-labelled Cyanokit by Methapharm Inc. and has added this product to the List of drugs for exceptional importation and sale (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-shortages/list.html).

In Canada, Cyanokit is an antidote indicated for the treatment of known or suspected cyanide poisoning.

The EU-labelled product is identical to the Canadian-authorized product having the **same active ingredient, strength, dosage form, route of administration, product formulation, and container volume.** However, the **Canadian Product Monograph has the following additional Warnings and Precautions that are not present in the EU-labelled product:**

- Hydroxocobalamin is teratogenic in animal model studies. Hydroxocobalamin levels were detected in urine for some patients up to 35 days following Cyanokit treatment indicating that elimination of Cyanokit from the body may not be completed after 35 days. Therefore, it is recommended to practice adequate methods of contraception for 2 months following Cyanokit treatment.
- Hydroxocobalamin may induce skin redness. It also absorbs visible light in the UV spectrum, and therefore has the potential to cause photosensitivity. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discoloured.

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Healthcare professionals are advised of the following:

- **The EU-labelled product should be used in the same manner as the Canadian-authorized product. Healthcare professionals should refer to the Canadian Product Monograph for Cyanokit (Hydroxocobalamin) 5 g/vial powder for infusion available in English and French on the Health Canada Drug Product Database (https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=86078) for information on the appropriate use of the product, including the indications, contraindications, warnings and precautions, special populations, adverse reactions, drug interactions, dosage and administration, storage conditions, and handling instructions.**
- The bilingual Canadian-authorized Cyanokit package insert and patient record label will be provided with the EU-labelled Cyanokit product.
  EU-labelled Cyanokit is labelled in multiple languages, including English and French.

Safety and security of Canadian and EU-labelled Cyanokit

It should be noted that the manufacturing of EU-labelled and Canadian-authorized Cyanokit has been temporarily suspended due to an investigation of a deviation involving a potential risk of microbial contamination of certain batches at the manufacturing site, which could compromise their sterility and lead to a potential risk of infection in patients receiving Cyanokit.

This interruption in manufacturing has resulted in a short-term drug shortage. To alleviate the critical drug shortage in Canada, EU-labelled Cyanokit, Lot # 2419 (Expiry Date: 03-Jul-2027), which was manufactured during the period affected by this deviation and is therefore potentially impacted, is being exceptionally imported into Canada for distribution. Lot # 2419 met the specifications for release, including those for sterility and endotoxin testing. No deviations that could be linked to the event have been identified during its manufacture. Although the risk of contamination of the affected lot cannot be completely excluded, it is considered minimal and is outweighed by the benefits of using Cyanokit in cases of acute suspected cyanide intoxication.

In view of the above, healthcare professionals should ensure that:

- Any sign or symptoms suggestive of systemic infection or sepsis (e.g. fever, persistent hypotension suggestive of shock) should trigger blood cultures and

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empiric antibiotic therapy to be adjusted to the identification of the pathogen and results of susceptibility testing.

- If blood culture reveal an unexpected microorganism, please contact the company to report it.

For additional information on the manufacturing deviation and other considerations for healthcare professionals regarding the use of affected lots of Cyanokit, please refer to Appendix 1 for a copy of the company's finalized DHPL titled *Hydroxocobalamin - Cyanokit® 5 g powder for solution for infusion – Important information regarding Cyanokit® in a context of shortage,* dated December 31, 2024.

Information on the imported product

Information on the imported product is summarised below.

Brand name	Dosage form, strength and route of administration	Product description and packaging	Country of authorization and identifying code	Foreign Market Authorization holder	Importer in Canada
Cyanokit	Powder for infusion, 5 g/vial hydroxocobalamin, for intravenous administration	Lyophilized powder in a colourless 250 mL glass vial closed with a bromobutyl rubber stopper and an aluminum cap with a plastic lid. Each pack contains 1 vial packed in a cardboard box, 1 sterile transfer device, 1 sterile intravenous infusion set and 1 sterile short catheter for administration to children.	Europe EU/1/07/420/002	SERB S.A. (Belgium)	Methapharm Inc.

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Additional information on the EU-labelled product for reference by healthcare professionals can be found in the Summary of Product Characteristics available in multiple languages including English and French at https://www.ema.europa.eu/en/medicines/human/EPAR/cyanokit#product-info.

Images of the EU-labelled product can be found in the Appendices 2 - 6. Healthcare professionals are advised that aspects of the inner and outer labels and packaging of the EU-labelled product may differ from Cyanokit marketed in Canada. **Proper selection of the intended product must be verified to avoid confusion with other products and prevent medication errors.**

The EU-labelled product does not have a drug identification number (DIN) or a barcode that scans in medication management systems in Canada. A facility-generated sticker may be required to enable barcode scanning and allow the product being dispensed and administered to be properly identified.

Reporting adverse drug reactions

Adverse drug reactions associated with the use of EU-labelled Cyanokit should be reported to the importer, Methapharm Inc., via telephone at 1-800-287-7686 ext. 7804 or email at medinfo@methapharm.com, or to Health Canada at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html or by calling toll-free at 1-866-234-2345.

Questions or concerns

For questions or concerns about EU-labelled Cyanokit, please contact Methapharm Inc. via telephone at 1-800-287-7686 ext. 7804.

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Appendix 1: **Dear Healthcare Professional Letter (Dec. 31, 2024)**

31 December 2024

Hydroxocobalamin - Cyanokit® 5 g powder for solution for infusion – Important information regarding Cyanokit® in a context of shortage.

Dear Healthcare Professional,

The marketing authorisation holder, SERB SA, in agreement with Methapharm Inc. and Health Canada would like to inform you of the following:

Summary

- **The manufacturing of Cyanokit® has been temporarily suspended due to an investigation of a deviation related to a risk of microbial contamination. The product is on a Drug Shortage in Canada.**
- **Manufacturing is expected to resume shortly; however, this interruption has resulted in a short term drug shortage. In order to alleviate the drug shortage in Canada, batches of Cyanokit® in scope of this event have been distributed in Canada.**
- **Although the risk of contamination of the affected batches cannot be completely excluded, it is minimal and outweighed by the benefits of using Cyanokit® in cases of acute suspected cyanide intoxication.**

- **In this context, SERB and Methapharm draw the attention of Healthcare Professionals likely to use a potentially impacted batch of Cyanokit® to the following points:**
  - **Cyanokit® should be reserved for patients presenting clinical signs of acute intoxication in a context suggestive of exposure to cyanide (inhalation of fire smoke or ingestion of a cyanide salt or cyanogenic product), including the following signs: cardiac arrest, shock, respiratory distress, coma, high lactic acidemia (>8 mmol/L).**
  - **Cyanokit® should not be used in the absence of signs of hypoxia.**
  - **Any sign or symptoms suggestive of systemic infection or sepsis (e.g. fever, persistent hypotension suggestive of shock) should trigger blood cultures and empiric antibiotic therapy to be adjusted to the identification of the pathogen and results of susceptibility testing.**

Background on the safety concern

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

The manufacturing of Cyanokit® 5 g powder for solution for infusion (hydroxocobalamin) is currently suspended due to an investigation of a deviation related to a risk of microbial contamination. Product batches in the table on next page were manufactured during the period impacted by this issue and are potentially impacted.

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Batch number	Expiry date	Market
2413	30-Oct-2026	Canada

The above-mentioned batches met the registered specifications for release, including sterility and endotoxin tests, and no deviations that could be linked to the event have been identified during their manufacture.

SERB Pharmaceuticals have generated a risk assessment, which demonstrated that it is not possible to eliminate all of the sterility assurance risk for the batches reviewed. However, it is concluded that based on the detailed batch by batch assessment, benefit of the product to patients, which is considered as critical in multiple markets, the potentially impacted batches should be made available for use.

This decision has been reached that the risk to patients created by the non-availability of potentially impacted product is considered a greater risk to public health versus making these batches available to the market.

No safety signals in relation with this quality defect have been reported at this stage. SERB Pharmaceuticals and Methapharm will continue to monitor the risk presented by this event using pharmacovigilance, customer complaint and medical information processes.

Since a risk of contamination, while minimal, cannot be fully ruled out, the purpose of this communication is to advise Healthcare Professionals to:

- Reserve Cyanokit® for patients presenting clinical signs of acute intoxication in a context suggestive of exposure to cyanide.
- Avoid using Cyanokit® in the absence of signs of hypoxia.
- Trigger blood cultures and empiric antibiotic therapy (to be adjusted to the identification of the pathogen and results of susceptibility testing) in presence of any sign or symptoms suggestive of systemic infection or sepsis (e.g. fever, persistent hypotension suggestive of shock).

Due to the time needed to implement corrective and preventive actions, normal manufacturing of Cyanokit® will not be able to resume for several weeks.

Call for reporting

Healthcare Professionals should report any adverse reactions suspected of being due to Cyanokit® to Methapharm Inc at:

Email: medinfo@methapharm.com

Phone: (+1)519-751-3602 Ext. 7804

Address: 81 Sinclair Blvd, Brantford, Ontario, N3S 76X, Canada

Healthcare professionals in Canada should report any suspected adverse reactions to the **Canada Vigilance Program**. This program is managed by Health Canada and is responsible for monitoring the safety of health products marketed in Canada.

1) **Online:** Submit a report through the MedEffect Canada website. Report a side effect of a health product, drug or medical device - Canada.ca
2) **Phone:** Call toll-free at **1-866-234-2345**

3) **Mail or Fax:** Complete a reporting form and send it by postage-paid mail or fax toll-free to **1-866-678-6789**

If you need more details on how to report, you can visit the MedEffect Canada section on the Health Canada website Adverse Reaction Reporting and Health Product Safety Information - Guide for Health Professionals - Canada.ca

Note: Cyanokit® is subject to additional monitoring for the risks "Clinical consequences of red coloration induced by hydroxocobalamin", "Laboratory test interferences" and "Device interaction".

The objective of this additional monitoring is to inform the Healthcare Professionals (HCP) about the above-listed risks and to improve their management.

This additional monitoring is an HCP educational sticker which is inside the Cyanokit® pack and includes the following wording: "To be attached to the patient's medical record: Cyanokit® has been administered in this patient. Cyanokit® may interfere with burn assessment (red coloration of skin) and laboratory tests and may lead to shut down of haemodialysis machines.

The current worldwide distribution of the Cyanokit® pack includes the same HCP educational sticker for all zones, in 25 languages.

Company contact points

If you have any questions, or require further medical information, please contact Methapharm Inc., Medical Information at:

Email: medinfo@methapharm.com

Phone: (+1)519-751-3602 Ext. 7804

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Appendix 2

Image of the EU-labelled Cyanokit

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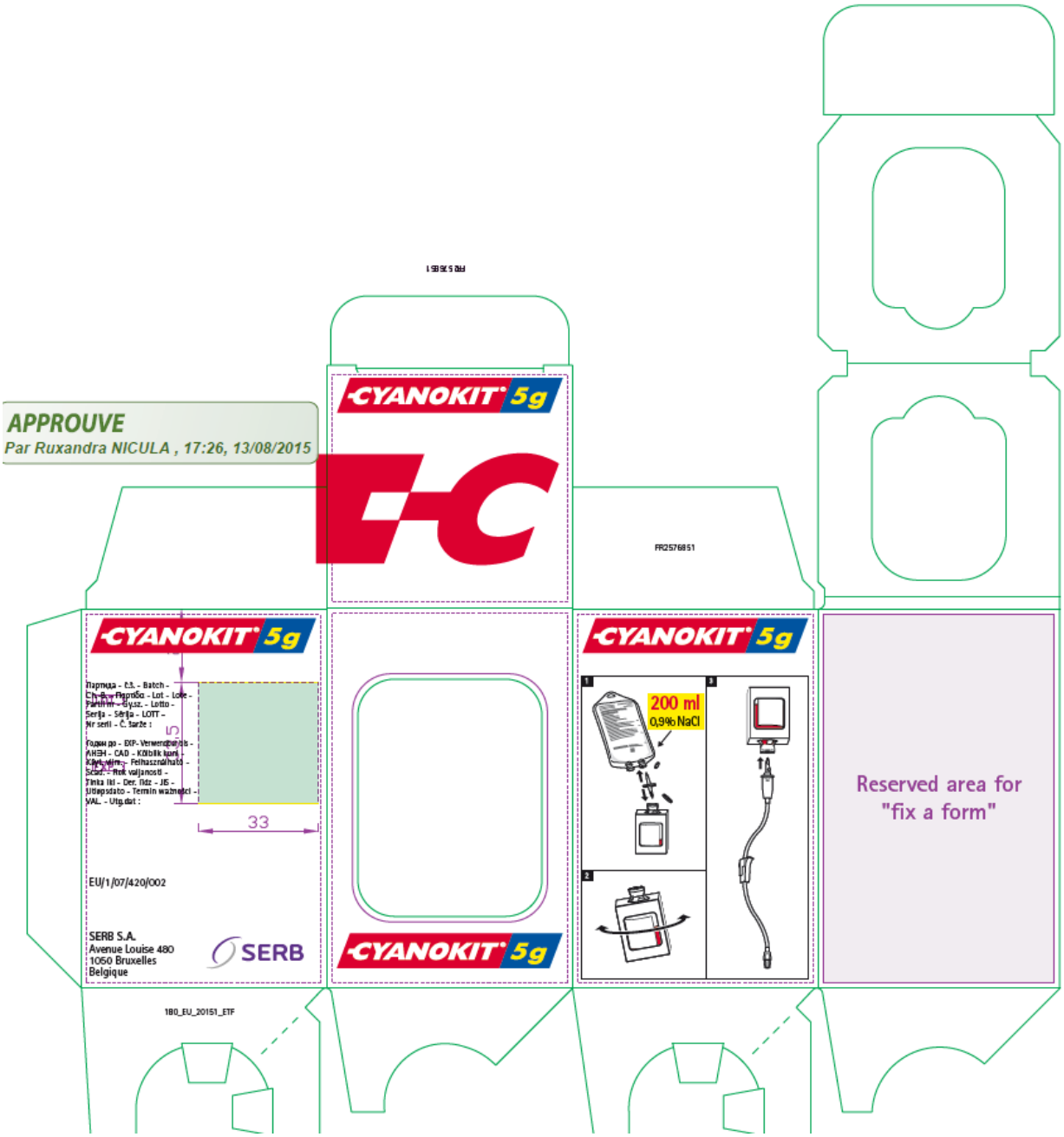
Appendix 3

Image of Inner Carton Label for EU-labelled Cyanokit (For an enlarged image of the section related to directions for use, please refer to image on the next page)



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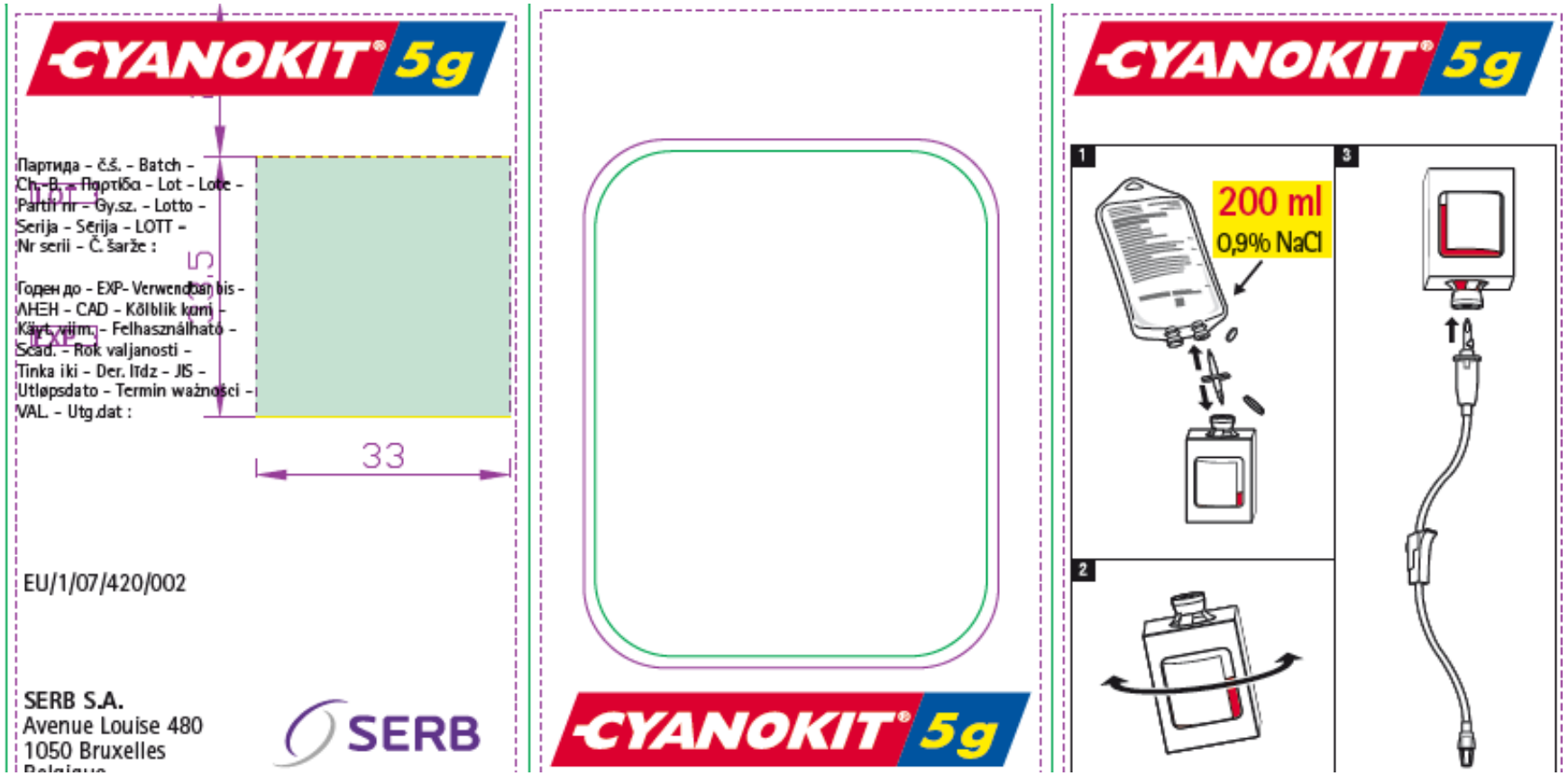
Appendix 4

Enlarged Image of Inner Carton label section (for EU-labelled Cyanokit) related to directions for use.



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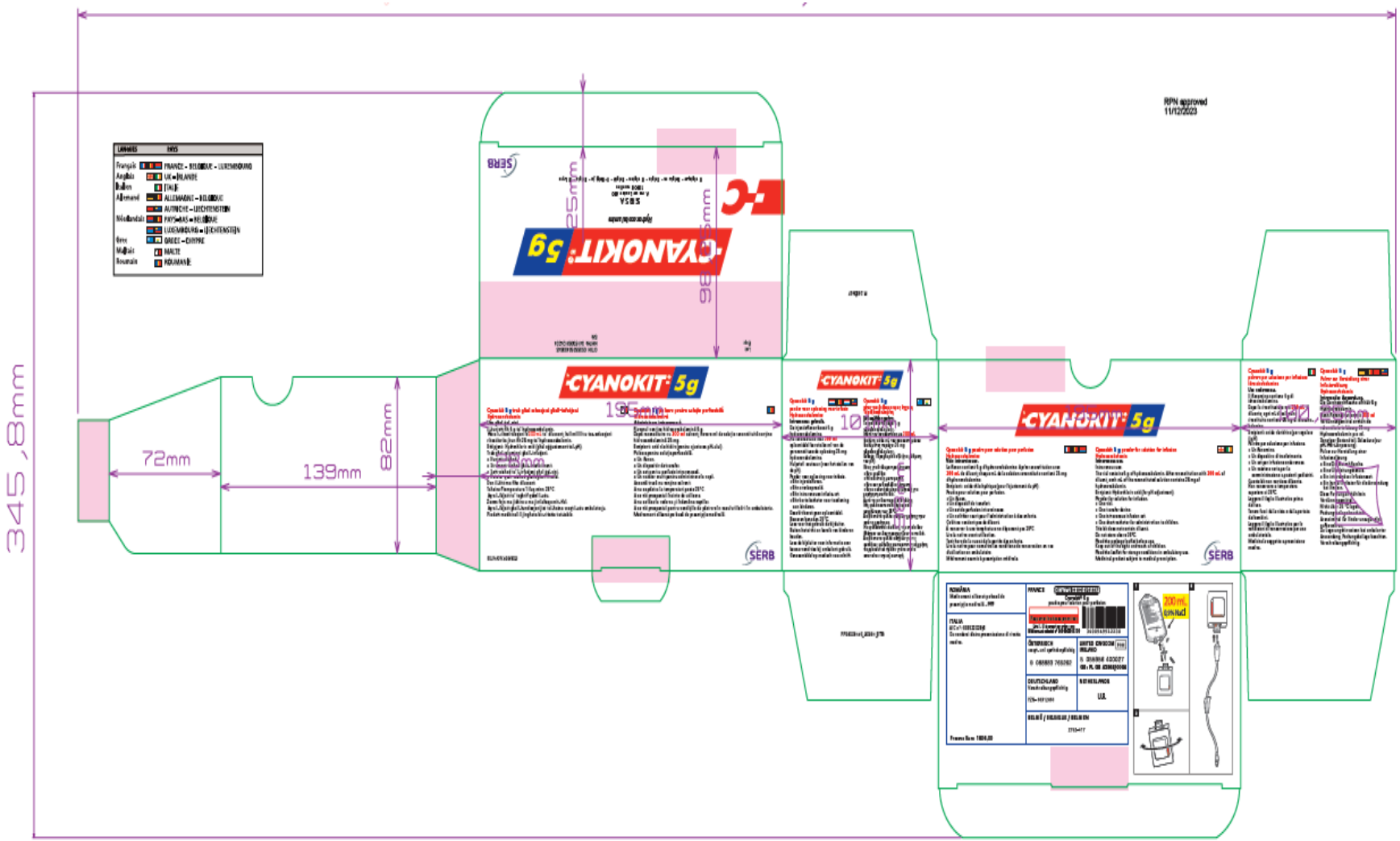
Appendix 5

Image of Outer Carton Label for EU-labelled Cyanokit (For enlarged image of the directions for use, please see next image)



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Appendix 6: Enlarged image of the outer carton label section (of the EU labelled Cyanokit) related to directions for use.

CYANOKIT® 5g

Cyanokit 5 g poudre pour solution pour perfusion
Hydroxocobalamine
Voie intraveineuse.
Le flacon contient 5 g d'hydroxocobalamine. Après reconstitution avec 200 mL de diluant, chaque mL de la solution reconstituée contient 25 mg d'hydroxocobalamine.
Excipient : acide chlorhydrique (pour l'ajustement du pH).
Poudre pour solution pour perfusion.
- Un flacon.
- Un dispositif de transfert.
- Un set de perfusion intraveineuse.
- Un cathéter court pour l'administration à des enfants.

Ce kit ne contient pas de diluant.
À conserver à une température ne dépassant pas 25°C.
Lire la notice avant utilisation.
Tenir hors de la vue et de la portée des enfants.
Lire la notice pour connaître les conditions de conservation en cas d'utilisation en ambulatoire.
Médicament soumis à prescription médicale.

Cyanokit 5 g powder for solution for infusion
Hydroxocobalamin
Intravenous use.
Intravenous use.
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.
Excipient: Hydrochloric acid (for pH adjustment).
Powder for solution for infusion.
- One vial.
- One transfer device.
- One intravenous infusion set.
- One short catheter for administration to children.

This kit does not contain diluent.
Do not store above 25°C.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Read the leaflet for storage conditions in ambulatory use.
Medicinal product subject to medical prescription.

SERB

ROMÂNIA
Medicament eliberat pe bază de prescripție medicală – PRF

ITALIA
AIC n°: 038632028/E
Da vendersi dietro presentazione di ricetta medica.

Prezzo: Euro 1606,00

FRANCE
N°Vert 0 805 626 997
Cyanokit® 5 g
poudre pour solution pour perfusion
Respecter les doses prescrites
Liste I - Uniquement sur ordonnance
Médicament autorisé n° 3400949912230
3400949912230

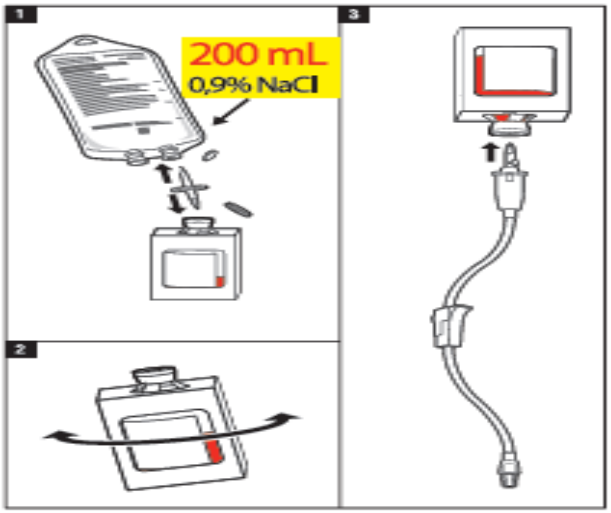
ÖSTERREICH
rezept- und apothekenpflichtig
9 088883 765262

UNITED KINGDOM
IRELAND
POM
5 055956 400027
GB: PL GB 43956/0004

DEUTSCHLAND
Verschreibungspflichtig
PZN – 06912400

NETHERLANDS
U.R.

BELGIË / BELGIQUE / BELGIEN
2762-417



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