

**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

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

## 1. NAME OF THE MEDICINAL PRODUCT

NORMOSANG 25 mg/ml, concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human hemin ..... 25 mg/ml.  
One ampoule of 10 ml contains 250 mg of human hemin.

After dilution of one 10 ml ampoule in 100 ml of 0.9% Na Cl solution, the diluted solution contains 2273 micrograms per ml of human hemin.

Excipient with known effect: ethanol 96% (1 g / 10 ml) (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

NORMOSANG is a dark coloured concentrate for solution for infusion.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyrinuria).

### 4.2. Posology and method of administration

#### Posology

The recommended daily dose is 3 mg/kg once daily for four days, diluted in 100 ml of 0.9% sodium chloride in a glass bottle and infused intravenously over at least 30 minutes into a large antebra- chial or central vein using an inline filter.

The dose should not exceed 250 mg (1 ampoule) per day.

Exceptionally, the course of the treatment may be repeated under strict biochemical surveillance if there is inadequate response after the first course of treatment.

#### *Elderly patients*

No dose adjustment is required.

#### *Children and adolescents*

Attacks of porphyria are rare in children but limited experience in tyrosinaemia suggests that it is safe to use a dose of not more than 3 mg/kg daily for 4 days, administered with the same precautions as for adults.

#### Method of administration

The infusions should be administered in a large antebra- chial or central vein over a period of at least 30 minutes. After the infusion, the vein should be rinsed with 100 ml of 0.9 % NaCl. It is recommended

to flush the vein initially with 3 to 4 bolus injections of 10 ml 0.9 % NaCl after which the remaining volume of saline can be infused for 10 - 15 minutes.

For instructions for the preparation of the solution, see section 6.6.

#### **4.3. Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

- Before treatment is started, it is necessary to confirm an attack of hepatic porphyria by series of clinical and biological criteria :
  - suggestive family or personal history,
  - suggestive clinical signs,
  - quantitative determination of urinary delta-amino-laevulinic acid and porphobilinogen (in preference to the classical WATSON-SCHWARZ or HOESCH tests, which are considered to be less reliable).
- The sooner NORMOSANG treatment is started after the onset of an attack, the greater its efficacy.
- As a result of NORMOSANG infusions, abdominal pain and other gastro-intestinal symptoms generally disappear within 2 - 4 days. Neurological complications (paralysis and psychological disorders) are less affected by the treatment.
- As porphyric attacks are often associated with various cardiovascular and neurological manifestations, appropriate monitoring should be ensured.
- It is also important to warn patients of the risk of attacks being worsened or triggered by fasting or taking certain medicinal products (particularly oestrogens, barbiturates and steroids), because by increasing the haem demand of the liver they are capable of indirectly inducing the delta-aminolaevulinic acid synthase activity.
- As the diluted solution is hypertonic, it should be administered by very slow intravenous infusion only.  
To prevent vein irritation, the infusion should be administered in at least 30 minutes in a large vein of the forearm or in a central vein.
- Venous thrombosis in the vein used for infusion may potentially occur following administration of NORMOSANG. There are few cases describing thrombosis at the caval vessels and their major tributaries (iliac and subclavian veins). The risk of thrombosis at the caval vessels cannot be excluded.
- Peripheral venous alterations have been reported after repeated infusions and can prevent the use of the affected veins for further infusions, necessitating the use of a central venous line. It is therefore recommended to rinse the vein with 100 ml of 0.9 % NaCl after the infusion.
- If intravenous cannula is in place for too long, due to mechanical irritation and also due to irritation by the injection fluid, vascular damage may occur which may lead to extravasation.
- Test the cannula before infusing NORMOSANG and also check it regularly during the infusion.
- In case of extravasation, skin discoloration may occur.

- Increased serum ferritin concentrations have been reported after repeated infusions. It is therefore recommended that serum ferritin be measured at regular intervals to monitor body iron stores. If necessary other investigation methods and therapeutic measures should be undertaken.
- The dark NORMOSANG colour may give the plasma an unusual colouring.
- Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations for specific markers of infections and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
- The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV.
- It is strongly recommended that every time that NORMOSANG is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.
- NORMOSANG contains 1 g of ethanol (96 %) per ampoule of 10 ml. This may be harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant woman and children. The ethanol content of NORMOSANG may modify or increase the effect of other medicines.
- NORMOSANG should not be used as a preventive treatment since available data is too limited and long term administration of regular infusions carries the risk of iron overload (see section 4.8. Undesirable effects).
- In addition to treatment with NORMOSANG and other necessary measures such as the elimination of triggering factors, ensuring a sufficient supply of carbohydrates is recommended.

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

During treatment with NORMOSANG the enzyme activity of the P450 enzymes increases. The metabolism of concomitantly administered drugs that are metabolised by cytochrome P450 enzymes (such as oestrogens, barbiturates and steroids) may increase during administration of NORMOSANG, leading to lower systemic exposure.

#### **4.6. Fertility, pregnancy and lactation**

##### Pregnancy

In the absence of specific experimental and clinical data, the risks during pregnancy are not defined; to date, however, no after-effects have been observed in new-born babies whose mothers were treated with NORMOSANG during their pregnancy.

##### Breast-feeding

NORMOSANG has not been studied during breast-feeding. However, since numerous substances are excreted in breast milk, it is appropriate to be cautious when administering NORMOSANG during lactation.

Due to limited data the use of NORMOSANG can not be recommended unless clearly necessary during pregnancy and breast-feeding.

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

There is no evidence to suggest that NORMOSANG affects adversely the ability to drive or use machines.

#### 4.8. Undesirable effects

The most commonly reported ADRs are infusion site reactions especially occurring if infusion takes place into veins which are too small (see section 4.4. Special warnings and precautions for use).

Reported adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

##### **Immune system disorders**

*Rare:* anaphylactoid reaction, hypersensitivity (such as dermatitis medicamentosa and tongue oedema).

##### **Nervous system disorders:**

*Not known:* headache

##### **Vascular disorders**

*Very common:* poor venous access

*Not known:* injection site thrombosis, venous thrombosis

##### **General disorders and administration site conditions**

*Common:* infusion site phlebitis, infusion site pain, infusion site swelling

*Rare:* pyrexia

*Not known:* injection site erythema, injection site pruritus, extravasation, injection site necrosis

##### **Investigations**

*Uncommon:* serum ferritin increased

*Not known:* blood creatinine increase

Increased serum ferritin concentrations have been reported after several years of treatment with repeated infusions, which may indicate an iron overload (see section 4.4. Special warnings and precautions for use).

##### **Skin disorders**

*Not known:* skin discoloration

##### 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 via the national reporting system listed in [Appendix V](#).

#### 4.9. Overdose

In animal experiments with NORMOSANG the acute toxic effects after high dosage were directed to the liver. Ten times higher total doses than the recommended human posology also decreased blood pressure in rats. High doses may cause disturbances in hemostasis.

NORMOSANG contains 4000 mg of propylene glycol per ampoule of 10 ml. Propylene glycol in high doses may cause central nervous system side-effects, lactic acidosis, kidney and liver toxicity, increase in plasma osmolarity, and haemolytic reactions.

Cases of overdosage with Normosang have been reported. For example, one patient had slight vomiting, pain and tenderness over the forearm (at the site of infusion) and made uneventful recovery. One other patient who received 10 ampoules of Normosang (2500 mg of human hemin) in a single

infusion developed fulminant hepatic failure and one patient with a medical history of chronic hepatic failure who received 4 ampoules of Normosang (1000 mg of human hemin) experienced acute liver failure requiring liver transplantation. One patient received 12 ampoules of Normosang (3000 mg of human hemin) over 2 days which resulted in hyperbilirubinemia, anemia and a generalised haemorrhagic diathesis. The effects lasted for several days after administration, but the patient then improved without consequences.

Also, a high dose (1000 mg) of haematin, another form of haem, has been reported to have caused transitory renal failure in one patient.

Blood coagulation parameters, hepatic, renal and pancreatic functions should be carefully monitored until their normalisation.

Cardiovascular monitoring should also be performed (possibility of arrhythmias).

#### Therapeutic measures

- Albumin infusions should be administered to fix the freely-circulating and potentially reactive hemin.
- The administration of activated charcoal will enable the enterohepatic recirculation of the haem to be interrupted.
- Haemodialysis is necessary to eliminate the propylene glycol.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Other hematological agents, ATC code: BO6AB.

Haem arginate is indicated for hepatic porphyria (intermittent acute porphyria, porphyria variegata and hereditary coproporphyria). These porphyrias are characterised by the existence of an enzymatic block in the pathway of haem biosynthesis resulting in:

- 1) a deficit of haem necessary for the synthesis of various haemoproteins.
- 2) mainly the accumulation ahead of the metabolic block of haem precursors which are directly or indirectly toxic to the organism.

The administration of hemin, by reducing the haem deficit, suppresses by feedback the activity of delta-amino-laevulinic synthase (the key enzyme in the synthesis of the porphyrins) which reduces the production of porphyrins and of the toxic precursors of haem. Therefore, by contributing to the re-establishment of normal levels of haemoproteins and of respiratory pigments, haem corrects the biological disorders observed in patients with porphyria. As the bioavailability of haem arginate is comparable to that of methaemalbumin, the natural form of transport of haem, it is effective both during remission and an acute attack. In both cases, but especially during an acute attack, hemin infusions are likely to correct the urinary excretion of delta-amino-laevulinic acid and porphobilinogen, the two main precursors whose accumulation is a characteristic of the disease. This applies for both acute intermittent porphyria and porphyria variegata.

Unlike older galenic preparations, haem arginate infusions do not cause any significant changes in the coagulation and fibrinolysis parameters in healthy volunteers. All these parameters have been shown to remain unchanged with the exception of the concentrations of factors IX and X, which fell temporarily by 10 to 15 %.

## 5.2. Pharmacokinetic properties

After an intravenous infusion of hemin (3 mg/kg), the pharmacokinetic parameters (mean  $\pm$  SD) observed in healthy volunteers and patients with porphyria are as follows:

- $C_{(0)}$  .....60.0  $\pm$  17  $\mu$ g/ml
- $t_{1/2}$  of elimination .....10.8  $\pm$  1.6 hours
- Total plasma clearance .....3.7  $\pm$  1.2 ml/min
- Volume of distribution .....3.4  $\pm$  0.9 l

After repeated infusions, the half-life of haem in the organism increases; it rises to 18.1 hours after the 4<sup>th</sup> infusion.

## 5.3. Preclinical safety data

Non-clinical data reveal no special effects for humans based on studies of safety pharmacology, single dose, repeated dose toxicity, mutagenicity, immunogenicity. Due to the human origin of NORMOSANG non-clinical studies with long-term treatment are not meaningful to perform therefore carcinogenic potential and toxicity to reproduction has not been investigated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Arginine,  
ethanol 96%,  
propylene glycol,  
water for injections.

### 6.2. Incompatibilities

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

### 6.3. Shelf-life

2 years.  
After dilution, the solution should be used within 1 hour.

### 6.4. Special precautions for storage

Store in a refrigerator (2°C – 8°C).  
Keep the ampoule in the outer carton in order to protect from light.  
For storage conditions after dilution of the medicinal product, see section 6.3.

### 6.5. Nature and contents of the container

10 ml of solution in ampoule (type I glass) - pack of 4.

### 6.6. Special precautions for disposal

#### *Preparation of the solution*

NORMOSANG, presented in ampoules, should be diluted immediately prior to administration in 100 ml of 0.9 % NaCl solution in a glass bottle; the amount of product required, calculated according to the patient's weight, is transferred from the ampoule to the glass bottle. The dilution should be prepared in a glass bottle because of slightly faster degradation of hemin in PVC plastic container.



Do not prepare more than one ampoule a day.

The solution should be used within the hour following dilution.

As the NORMOSANG solution is dark coloured even after dilution, it is difficult to verify visually the absence of particles in suspension. It is therefore recommended to use an infusion set with a filter.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Recordati Rare Diseases  
Immeuble "Le Wilson"  
70 avenue du Général de Gaulle  
F-92800 Puteaux  
France

## **8. MARKETING AUTHORISATION NUMBER**

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

Date of first authorisation:  
Date of latest renewal: 5 May 2019

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

12 December 2019

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE  
SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S)  
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING  
AUTHORISATION HOLDER**

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND  
MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH  
RELEASE**

**Name and address of the manufacturer(s) of the biological active substance(s)**

**PCAS FINLAND OY**  
MESSUKENTÄNKATU 8  
20210 TURKU  
FINLAND

**Name and address of the manufacturer(s) responsible for batch release**

**RECORDATI RARE DISEASES**  
IMMEUBLE LE WILSON  
70, AVENUE DU GENERAL DE GAULLE  
F-92800 PUTEAUX  
FRANCE

**B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION  
REGARDING SUPPLY OR USE**

- **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**

Not applicable.

**C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING  
AUTHORISATION HOLDER**

Not applicable.

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

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON TEXT**

**1. NAME OF THE MEDICINAL PRODUCT**

NORMOSANG 25 mg/ml, concentrate for solution for infusion.  
Human hemin

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

Human hemin .....25 mg/ml.  
One ampoule of 10 ml contains 250 mg human hemin.

After dilution of one 10 ml ampoule in 100 ml of 0.9% Na Cl solution, the diluted solution contains 2273 micrograms per ml of human hemin.

**3. LIST OF EXCIPIENTS**

Ethanol 96 % (See leaflet for further information), arginine, propylene glycol, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion (250 mg/10 ml in ampoule – pack size of 4)

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

**Intravenous use.**

*By very slow intravenous infusion only (at least over 30 minutes).*

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

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

**SPECIAL WARNING:** Must be diluted before use, see leaflet.

**8. EXPIRY DATE**

EXP: {MM-YYYY}

After dilution, the solution should be used within 1 hour.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).

Keep the ampoule in the outer carton in order to protect from light.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

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

Recordati Rare Diseases  
Immeuble “Le Wilson”  
70 avenue du Général de Gaulle  
F-92800 Puteaux  
France

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

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

<b>18.    UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
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PC:  
SN:  
NN:



**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**TEXT FOR AMPOULE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

NORMOSANG 25 mg/ml, concentrate for solution for infusion.  
Human hemin  
**Intravenous use**

**2. METHOD OF ADMINISTRATION**

**Must be diluted before use. After dilution, use within 1 hour.**  
Read the package leaflet before use.

**3. EXPIRY DATE**

EXP : {MM-YYYY}

**4. BATCH NUMBER**

Batch:

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

**250 mg of hemin in 10 ml**

**6. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### **NORMOSANG 25 mg/ml, concentrate for solution for infusion** Human hemin

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What NORMOSANG is and what it is used for
2. What you need to know before you use NORMOSANG
3. How to use NORMOSANG
4. Possible side effects
5. How to store NORMOSANG
6. Contents of the pack and other information

#### **1. What NORMOSANG is and what it is used for**

NORMOSANG contains human hemin, which is a substance derived from human blood. NORMOSANG is used to treat sudden attacks that occur in patients suffering from acute hepatic porphyria; the disease is characterized by liver accumulation of compounds (including porphyrins and its toxic precursors). There are three types of hepatic porphyria whose medical names are: acute intermittent porphyria, porphyria variegata and hereditary coproporphyria. This accumulation leads to symptoms of the disease including pain (mainly abdomen, back and thighs), nausea, vomiting and constipation.

#### **2. What you need to know before you use NORMOSANG**

##### **Do not use NORMOSANG:**

- if you are allergic to human hemin or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

- Before treatment with NORMOSANG, your doctor should confirm an attack of hepatic porphyria by series of clinical and biological criteria :
  - suggestive family or personal history;
  - suggestive clinical signs;
  - quantitative determination of delta-amino-laevulinic acid and porphobilinogen (specific markers of the disease) in urines.
- The sooner NORMOSANG treatment is started after the onset of an attack, the greater its efficacy.
- As a result of NORMOSANG infusions, abdominal pain and other gastro-intestinal symptoms generally disappear within 2 - 4 days. Neurological complications (paralysis and psychological disorders) are less affected by the treatment.

- You will be monitored during the whole course of the treatment, because porphyria attacks are often associated with various effects on the heart and circulation, and on the nervous system.
- Do not:
  - make sudden changes to your normal diet, in particular, do not stop eating for long periods
  - take drugs or substances such as oestrogens (e.g. oral contraceptives), barbiturates (drugs which help you to sleep and drugs sometimes used to treat epilepsy) or steroids (body hormone-like drugs), because this can bring on an attack or make the attack worse.

*Please ask your doctor or pharmacist for advice on the drugs and substances you should not take (now and in the future).*

- To prevent vein irritation, the solution will be administered by infusion in a large vein (blood vessel) of your arm or in a vein in your chest over a period of at least 30 minutes. After the infusion, the vein shall be rinsed with a saline solution.
- A blood clot (known as a ‘venous thrombosis’) can block the vein used for infusion.
- If your cannula is in place for long time, vascular damage may occur and could lead to an unintended migration of NORMOSANG outside the vein (extravasation). This migration may cause a skin discolouration.
- In order to diminish the risk of extravasation, the nurse/doctor will test your cannula before the infusion and will check it regularly during the infusion.
- The infused solution can give your blood an unusual colour.
- To limit the risk of iron compound increase, NORMOSANG should not be used as a preventive treatment of the acute attacks.
- Human hemin contains iron. It can sometimes happen that iron builds up in the body after several years of treatment with repeated infusions of NORMOSANG. Your doctor may perform blood tests from time to time to check the level of iron in your body.
- Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations for specific markers of infections and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
- The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. It is strongly recommended that every time that NORMOSANG is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product

#### **Other medicines and NORMOSANG**

Do not take drugs or substances such as oestrogens (e.g. oral contraceptives), barbiturates (drugs which help you to sleep and drugs sometimes used to treat epilepsy) or steroids (body hormone-like drugs), because they can bring on an attack or make the attack worse.

Tell your doctor if you are taking, have recently taken or might take any other medicines.

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

It is not known if there is a risk in using the medicine during pregnancy. However, mothers treated with have delivered normal babies.

When you are pregnant, ask your doctor for advice before NORMOSANG is administered to you. Your doctor will only prescribe the medicine when absolutely necessary.

NORMOSANG has not been studied during breast-feeding. However, since a lot of drugs are passed into the breast-milk, you should inform your doctor when you are breast-feeding and ask for advice before NORMOSANG is administered to you. Your doctor will only prescribe NORMOSANG treatment when absolutely necessary, or may advise you to stop breast-feeding.

NORMOSANG contains ethanol (alcohol). This should be taken into account if you are pregnant or breast feeding women. See heading "Important information about some of the ingredients of NORMOSANG".

### **Driving and using machines**

Your medicine should not affect your ability to drive or to use machines.

### **Important information about some of the ingredients of NORMOSANG**

NORMOSANG contains 11.78 vol. % ethanol (alcohol), i.e. up to 1000 mg per daily dose (one ampoule), equivalent to 23.6ml beer or 9.8ml wine per daily dose.

This can be harmful for those suffering from alcoholism. To be taken into account in pregnant or breast feeding women, children and high risk groups such as patients with liver disease, or epilepsy.

*Ask your doctor for advice before NORMOSANG is administered to you, if you suffer from one of the above conditions.*

## **3. How to use NORMOSANG**

The medicine will only be administered to you in a hospital setting by qualified hospital personnel.

The dose to be administered will be calculated from your body weight and is about 3 mg per kg of body weight per day, but not more than 250 mg (1 ampoule) per day. This calculated amount will be diluted with a saline solution (0.9 % sodium chloride) in a glass bottle and this will form a dark coloured solution.

The solution will be administered by infusion in a large vein (blood vessel) of your arm or in a vein in your chest over a period of at least 30 minutes. The infused solution can give your blood an unusual colour.

After the infusion, the vein shall be rinsed with a saline solution.

Usually, you will receive one infusion per day during four days.

If after this first course of treatment the symptoms are not relieved, your doctor can decide exceptionally to start a second course of treatment.

### **If you have received more NORMOSANG than it should**

If you have received more NORMOSANG than you should have, your doctor will treat you to prevent harmful effects.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

*Rare (may affect up to 1 in 1,000 people):*

- Fever and serious allergic reactions (rash, tongue swelling) including anaphylactoid reaction may rarely occur.

Anaphylactoid reactions are sudden and potentially life-threatening reactions that may rarely occur. If you suffer symptoms such as facial oedema, dyspnoea, tightness in the chest, tachycardia, low blood pressure, urticaria, spontaneous loss of consciousness (caused by insufficient blood to the brain), the infusion must be stopped and the doctor must be contacted immediately.

*Very common (may affect more than 1 in 10 people):*

- After repeated treatments, access to veins in your arm may become difficult, which may mean that a tube needs to be placed in a chest vein.

*Common (may affect up to 1 in 10 people):*

- If administered in too small a vein, pain and inflammation can be caused.

*Uncommon (may affect up to 1 in 100 people):*

- The amount of an iron compound (called ferritin) may increase in the blood following repeated treatments over several years. To limit the risk of iron compound increase, NORMOSANG should not be used as a preventive treatment of the acute attacks.

*Frequency not known (frequency cannot be estimated from the available data):*

- Headache.
- Venous thrombosis (clots formation in the peripheral or central veins) including injection site thrombosis.
- Leakage of the infusion to the surrounding tissue (extravasation).
- Skin damage (necrosis).
- Skin redness on the site of injection (injection site erythema).
- Skin itching on the site of injection (injection site pruritus).
- Increase in the blood level of creatinine (substance excreted by the kidneys).
- Skin discoloration.

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store NORMOSANG**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the ampoule label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the ampoule in the outer carton in order to protect from light.

After dilution, the solution should be used within 1 hour.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What NORMOSANG contains**

- The active substance is human hemin (25 mg/ml). 10 ml ampoule contains 250 mg of human hemin. After dilution of one 10 ml ampoule in 100 ml of 0.9 % NaCl solution, the diluted solution contains 2273 micrograms per ml of human hemin.
- The other ingredients are arginine, ethanol (96 %), propylene glycol and water for injections.

### **What NORMOSANG looks like and contents of the pack**

NORMOSANG is presented as a Concentrate for solution for infusion (10 ml in ampoule – pack size of 4). NORMOSANG is a dark coloured solution even after dilution of the concentrate for solution for infusion.

### **Marketing Authorisation Holder**

Recordati Rare Diseases  
Immeuble “Le Wilson”  
70 avenue du Général de Gaulle  
F-92800 Puteaux  
France

### **Manufacturer**

Recordati Rare Diseases  
Immeuble “Le Wilson”  
70 avenue du Général de Gaulle  
F-92800 Puteaux  
France

Or

Recordati Rare Diseases  
Eco River Parc  
30, rue des Peupliers  
F-92000 Nanterre  
France

### **This medicinal product is authorised in the Member States of the EEA under the following names:**

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Human Hemin Orphan Europe - Poland

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