

NORMOSANG® 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 hemin25 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.

Excipients: ethanol 96% (1 g / 10 ml) (see section 4.4).

For a 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 coproporphyria).

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 antebachial 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 antebachial 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. Contra-indications

Hypersensitivity to the active substance or to any of the excipients.

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.
- 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.
- 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. Interactions with other medicaments 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. Pregnancy and lactation

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.

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 (>10%), common (1-10%), uncommon (0.1-1%), rare (0.01-0.1%).

Immune system disorders

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

Vascular disorders

Very common: Poor venous access.

General disorders and administration site conditions

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

Rare: Pyrexia.

Investigations

Uncommon: Serum ferritin increased.

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).

Post-marketing experience:

Nervous system disorders:

Frequency unknown: headache.

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 /10 ml of propylene glycol (per ampoule). 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.

Three cases of overdosage with Normosang have been reported. In two cases the label was misread and the patients were given ten times the recommended dose. One patient made uneventful recovery. She had slight vomiting, pain and tenderness over the forearm (at the site of infusion). The other patient who received an overdosage of Normosang (2500 mg) in a single infusion developed fulminant hepatic failure. One patient received six ampoules of Normosang a day for two days (3000 mg over 2 days) which resulted in hyperbilirubinemia, anaemia 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 μ 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 4th 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 of the diluted 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 product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orphan Europe
Immeuble "Le Wilson"
70 avenue du Général de Gaulle
F-92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER

Mutual Recognition Procedure (MRP) n° FR/H/140/01
National Marketing Authorisation numbers depending on the country

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation:

- Initial MRP: 5 May 1999
- Repeat use MRP: 13 June 2006

Date of last renewal: 7 May 2009

10. DATE OF REVISION OF THE TEXT