SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hemin 25 mg/ml.

One ampoule of 10 ml contains 250 mg of 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 hemin.

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

Sugar free.

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

NORMOSANG is indicated for the treatment of acute attacks of hepatic porphyrias (acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria).

4.2 Posology and method of administration

Posology

Treatment should be started without delay as soon as it has been established that the symptoms are caused by porphyria. During NORMOSANG therapy other measures normally involved in the treatment of acute porphyria,

such as adequate nutrition and elimination of provocative factors, are still indicated. See section 4.4 Special warnings and precautions for use.

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 antebrachial or central vein using an inline filter. See table below.

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.

Dosage and administration according to body weight:

Weight, kg	**Amount haem, mg (kg x 3 mg/kg)**	**NORMOSANG solution from the ampoule, ml**	**NORMOSANG + saline solution infused, ml**
40	120	4.8	104,8
45	135	5.4	105,4
50	150	6.0	106,0
55	165	6.6	106,6
60	180	7.2	107,2
65	195	7.8	107,8
70	210	8.4	108,4
75	225	9.0	109,0
80	240	9.6	109,6

Elderly patients

No dose adjustment is required.

Children and adolescents

Attacks of porphyria are rare in children. The safety and efficacy of NORMOSANG in children and adolescents have not been established.

Method of administration

The infusion is given in a large antebrachial 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 during 10 – 15 minutes. For instructions for the preparation of the solution, see section 6.6.

4.3 Contraindications

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

The safety of NORMOSANG in children and nursing women have not been established.

4.4 Special warnings and precautions for use

Before treatment is started, it is necessary to confirm an attack of hepatic porphyria by a series of clinical and biological criteria:

- suggestive family or personal history
- suggestive clinical signs
- quantitative determination of urinary delta-aminolaevulinic acid and porphobilinogen (in preference to the classical WATSON-SCHWARZT 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 gastrointestinal 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 a 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 flush the vein with 100 ml 0,9 % NaCl after the infusion.

If the 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 medicines 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 medicines 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 (see section 4.2 Posology).

4.5 Interaction with other medicines and other forms of interaction

During treatment with NORMOSANG the enzyme activity of the P450 enzymes increases. The metabolism of concomitantly administered medicines 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.

Breastfeeding

NORMOSANG has not been studied during breastfeeding.

Due to limited data the use of NORMOSANG cannot be recommended during lactation (see section 4.3).

Fertility

No fertility data is currently available.

4.7 Effects on 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

a) Summary of the safety profile

The most commonly reported ADRs are infusion site reactions, such as pain, swelling (common) and thrombophlebitis (common), 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

b) Tabulated list of adverse reactions

Immune system disorders	
Rare:	anaphylactoid reaction, hypersensitivity reactions (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 also 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Company contact details to which suspected adverse reactions may be reported:

Equity Pharmaceuticals (Pty) Ltd

24 Hour telephone number: +27 (0) 12 345 1747

4.9 Overdose

The major safety margin against overdose is the binding of haem by plasma proteins (haemopexin, albumin), which is normally saturated with about 2,5 g of hemin.

Symptoms of overdose include vomiting, fulminant hepatic failure, hyperbilirubinaemia, anaemia, haemostasis, and a generalised haemorrhagic diathesis.

NORMOSANG contains 4 000 mg of propylene glycol per 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.

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

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

Therapeutic measures:

The following strategy, based on theoretical calculations, may be followed:

- Albumin infusions should be administered to bind 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.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 34. Other

Pharmacotherapeutic group: Other haematological 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.

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 ± SD) observed in healthy volunteers and patients with porphyria are as follows:

$C_{(0)}$: 60,0 ± 17 µg/ml

t½: 10,8 ± 1,6 hours

Total plasma clearance: 3,7 ± 1,2 ml/min

Volume of distribution: 3,4 ± 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine

ethanol 96 %

propylene glycol

water for injections.

6.2 Incompatibilities

NORMOSANG must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

3 years

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

6.4 Special precautions for storage

Store in a refrigerator (2 ºC - 8 ºC).

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 container

10 ml of solution in a colourless glass ampoule with a white break ring – pack of 4.

6.6 Special precautions for disposal and other handling

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 portion of the infusion concentrate or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

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Nellmapius Drive, Irene

South Africa

8 REGISTRATION NUMBER

Z/34/19

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 October 1991

10 DATE OF REVISION OF TEXT

02 June 2021