

Registration number:
34/30.4/0261

Proprietary name:
HEMOPURE®

Descriptive name of medicine:
haemoglobin glutamer-250 (bovine)

Pharmacological classification:
A 30.4 - Biologicals - Other

Scheduling status:
S4

Composition:
Hemopure® contains 13g/dL polymerized haemoglobin of bovine origin (active substance) in a modified Lactated Ringer's Solution containing Water for Injection USP 100g/dL, NaCl USP 115mmol/L, KCl USP 4mmol/L, CaCl₂·2H₂O USP 1.4mmol/L, NaOH NF 13mmol/L, Sodium Lactate USP 27mmol/L, N-acetyl-L-cysteine USP 200mg/dL.

Identification:
Transparent infusion bags containing a sterile clear deep purple solution, free from particles. The infusion bags are enclosed in an airtight aluminium foil overwrap.

Pharmacological action of the medicine:
Hemopure® is an oxygen carrying fluid that increases plasma and total haemoglobin (Hb) concentrations. Hemopure® has a right shifted oxygen equilibrium curve with a p50 of 36torr. When fully saturated, it binds approximately 1.36mL of oxygen per gram of haemoglobin.

Experimental studies in animals have demonstrated that Hemopure® increases arterial oxygen content and delivers oxygen to hypoxic tissues in a dose dependent manner, and resuscitates animals in shock.

A plasma haemoglobin concentration of $\geq 0.6\text{g Hb/kg}$ (total Hb dose of $\geq 45\text{g}$) is associated with greater than 20% increase in arterial oxygen content and a 10-15% enhancement of pulmonary diffusing capacity over baseline. Hemopure® provides an oxygen treatment bridge and eliminates the need for red blood cell transfusions in surgical patients.

Pharmacokinetics:
The plasma clearance of Hemopure® has been shown to follow first order pharmacokinetics for either single or multiple dosage regimens. At a dosage of 45g Hb, the plasma elimination half-life of Hemopure® is approximately 20 hours with a clearance of approximately 0.12L/hr. Plasma concentrations of haemoglobin are proportional to dose.

Indications:
Hemopure® is indicated for the treatment of adult surgical patients who are acutely anemic. Hemopure® is indicated for the purpose of eliminating, delaying or reducing the need for allogenic red blood cells.

Contra-Indications:
Hemopure® is contraindicated in patients with known hypersensitivity to bovine haemoglobin and in patients with the rare condition of systemic mastocytosis. Because Hemopure® is a plasma volume expander, administration should be carefully monitored in patients who are at risk for adverse effects from fluid administration. Uncontrolled hypertension. The safety of Hemopure® has not been established in pregnant and lactating women. Administration of Hemopure® to pregnant women is not recommended.

Dosage and directions for use:
It is recommended that Hemopure® be administered as an 'oxygen bridge'. In adults an oxygen bridge is established by an initial loading dose of 60g (2 units) of Hemopure® followed by periodic infusions of 30-60g (1-2 units) of Hemopure®, not to exceed a total dose of 210g (7 units). Following the initial loading dose, subsequent doses should be approximately 30 grams and guided by clinical signs and symptoms of anaemia and body weight. The need for additional Hemopure® administration should be assessed daily and as clinically indicated. Treatment may be discontinued when the haematocrit is at least 18%, although a higher haematocrit may be desirable in some patients.

The rate of administration is typically 1g/minute but should be guided by the patient's clinical condition. Hemopure® can be given at a higher rate if necessary. Remove the overwrap prior to use and use within 24 hours. Hemopure® should be administered using aseptic technique via a standard intravenous infusion set and catheter through a central or peripheral vein. Do not administer with other fluids or drugs in the same infusion set. Do not add medications or other solutions to the bag. Do not combine the contents of more than one bag.

Use of Hemopure® does not require cross matching with recipient blood. A blood transfusion is not contraindicated in patients who receive Hemopure®.

Side-effects and special pre-cautions:
Side-effects that show a $\geq 5\%$ absolute difference in incidence comparing Hemopure® and control groups include abdominal pain, asthenia, lab test abnormality, pain, hypertension, jaundice, nausea, rash and haematuria.

Jaundice and hypertension have been reported in a substantially increased frequency in patients receiving Hemopure®. Jaundice is an expected side-effect from the processing

of haemoglobin to bilirubin. It does not appear to be associated with liver dysfunction. Mean increases in systolic and diastolic arterial blood pressures with Hemopure® are modest (~ 16 and $\sim 11\text{mmHg}$ respectively).

Transient mild to moderate isolated increases in enzyme levels, usually aspartate transaminase, alanine transaminase, or lipase, may occur after Hemopure® administration and are not associated with clinical hepatitis or pancreatitis.

Cardiovascular events occurring in $< 2\%$ of patients treated with Hemopure® include angina, arterial thrombosis, myocardial ischemia, myocardial infarction, and congestive heart failure.

The following events, which are also expected sequelae of surgical procedures, were seen in Hemopure® clinical trials: asthenia (fatigue/weakness), chills, oedema, fever, headache, post-operative pain (incisional), arrhythmias (including atrial fibrillation), bradycardia, decreased blood pressure, elevated blood pressure, tachycardia, abdominal gas, constipation, diarrhoea, ileus, nausea, vomiting, hypocalcaemia, hypokalaemia, hypomagnesaemia, confusion, decreased mental activity, insomnia, (b)basilar crackles/rales, decreased breath sounds, arterial desaturation, hypoxaemia, respiratory insufficiency/hypercarbia, sore throat, itching, rash, wound drainage, difficulty urinating/oliguria and haematuria.

Serum and plasma samples from patients administered Hemopure® will have a red colour due to the haemoglobin. This may result in artifactual increases or decreases in the results of clinical laboratory tests, depending on the type of analyser and reagents used. Accurate reading of bilirubin or albumin cannot be obtained with any instrument if Hemopure® is present in the plasma or serum. The Hitachi clinical chemistry analyser is accurate for electrolytes, blood urea nitrogen, creatine kinase, glucose, alanine transaminase and aspartate transaminase. The Johnson & Johnson Ektachem is accurate for electrolytes, blood urea nitrogen, creatine kinase, glucose, alanine transaminase, aspartate transaminase and lipase. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) can be accurately determined using methods that are mechanical, magnetic, and light scattering. Optical methods are not reliable for coagulation assays in the presence of Hemopure®. There is no interference with haematology or urinalysis testing.

Pulse oximetry values may decrease slightly after the infusion of Hemopure® due to the right shifted oxygen equilibrium curve of Hemopure® compared with human red blood cells. The arterial partial pressure of oxygen is not affected by Hemopure®.

Care should be taken while administering Hemopure®, which is an isoncotic colloid solution. As with any colloid, avoidance of circulatory overload is an important consideration. Although clinical trial data have not conclusively demonstrated adverse effects in patients with heart failure, these patients should be assessed for fluid overload particularly during and after the administration of doses exceeding 60 grams in one day. Concomitant administration of other colloids (such as plasma and hetastarch) should be undertaken with caution to avoid fluid overload.

The safety of Hemopure® for more than one treatment period, defined as less than or equal to six days, has not been established. The safety of Hemopure® in pregnant or lactating females has not been determined. The use in such females is not recommended.

There are insufficient data to support the use of Hemopure® in children.

If an immediate hypersensitivity reaction occurs, infusion of Hemopure® should be immediately discontinued and appropriate treatment administered.

Known symptoms of overdose and particulars of its treatment:
Overdose or excessive rate of administration of Hemopure®, a colloid, may result in circulatory overload manifested by pulmonary oedema and/or peripheral oedema. If these symptoms occur, stop the infusion of Hemopure® and institute usual supportive treatment.

Presentation:
250mL (30g) haemoglobin glutamer-250 (bovine) 13g/dL in a clear infusion bag sealed in an aluminium overwrap bag.

Storage Instructions:
Store at 2-30°C in overwrap. Do not freeze.

Use within 24 hours after opening overwrap.
Do not add medications or other solutions to the bag.
Keep out of reach of children.

Name and Business address of Applicant:

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Registrasie nommer:

34/30.4/0261

Handelsnaam:

HEMOPURE®

Beskrywende naam van medisyne:

hemoglobien glutameer-250 (bees)

Farmakologiese klassifikasie:

A30.4 - Biologiese middels - Ander

Skeduleringstatus:

S4

Samestelling:

Hemopure® bevat 13g/dL gepolimeriseerde hemoglobien van bees oorsprong (aktiewe substans) in 'n gemodifiseerde Ringer se laktaatoplossing wat uit die volgende bestaan: Water vir inspuiting USP 100g/dL, NaCl USP 115mmol/L, KCl USP 4mmol/L, CaCl₂-2H₂O USP 1.4mmol/L, NaOH NF 13mmol/L, Natriumlaktaat USP 27mmol/L, N-asetiel-L-sisteïen USP 200mg/dL.

Identifikasie:

'n Deurskynende infuussak wat 'n steriele helder donkerpers oplossing, sonder enige deeltjies, bevat. Die infuussakke is verseël in 'n lugdigte foelie omhulsel.

Farmakologiese werking van die medisyne:

Hemopure® is 'n suurstofdraende vloeistof wat plasma en totale hemoglobien (Hb) konsentrasies verhoog. Hemopure® het 'n suurstofewigskurwe wat na regs beweeg met 'n p50 van 36torr. Wanneer dit ten volle versadig is, is die gebonde hoeveelheid suurstof omtrent 1.36mL suurstof per gram hemoglobien.

Eksperimentele studies in diere het aangetoon dat Hemopure®, op 'n dosis afhanklike manier, die arteriële suurstof inhoud verhoog en ook suurstof lewer aan hipoksiese weefsels. Diere wat aan skok lei, is geresusiteer.

Wanneer die plasma hemoglobien konsentrasie ≥ 0.6 Hb/kg (totale Hb dosis van ≥ 45 g) bereik, is die arteriële suurstofinhoud met meer as 20% verhoog en pulmonêre difuus kapasiteit met 10-15% verhoog, vanaf basislyn. Hemopure® verskaf 'n suurstofbrug en skakel die behoefte aan rooibloedseloortappings in sjiurgiese pasiënte uit.

Pharmakokinetika:

Daar is aangetoon dat die plasma opruiming van Hemopure® volgens eerste orde farmakokinetika, vir beide enkel of meervoudige doserings, plaasvind. Teen 'n dosis van 45g Hb, is die plasma eliminasië halfleeftyd omtrent 20 uur, met 'n opruiming van omtrent 0.12L/hr. Die plasma konsentrasies van Hemopure® is eweredig tot die dosis.

Indikasies:

Hemopure® is geïndikeerd vir die behandeling van akute anemie in volwasse sjiurgiese pasiënte. Hemopure® elimineer, vertraag of verminder die behoefte aan allogeeniese rooibloedseloortappings.

Kontra-indikasies:

Hemopure® is teenaangedui in pasiënte met 'n bekende hipersensitiwiteit vir bees hemoglobien en in pasiënte met sistemiese mastosistose, 'n toestand wat baie selde voorkom. Hemopure® is 'n plasma volume uitsetter en daarom moet pasiënte vir wie vloeistofaanvullings 'n potensiele risiko inhou, baie sorgvuldig gemonitor word. Ongekontroleerde hipertensie. Die veiligheid van Hemopure® in swanger en lakterende vroue is nie bewys nie. Die toediening van Hemopure® aan swanger vroue word nie aanbeveel nie.

Dosis en gebruiksaanwysings:

Dit word aanbeveel dat Hemopure® toegedien word as 'n "suurstofbrug". In volwassenes word die suurstofbrug tot stand gebring deur 'n aanvangsdosis van 60g (2 eenhede) Hemopure®, gevolg deur die periodieke infuus van 30-60g (1-2 eenhede) Hemopure®. 'n Totale dosis van 210g (7 eenhede) moet nie oorskry word nie. Opvolgdosisse, na die aanvangsdosis, sal omtrent 30g wees, en sal afhang van die kliniese tekens en simptome van anemie en liggaamsmassa. Die toediening van addisionele dosisse Hemopure® moet daagliks heroorweeg word op grond van kliniese behoeftes. Toediening kan gestaak word as die hemokrit ten minste 18% is, alhoewel 'n hoër waarde wenslik mag wees in sommige pasiënte.

Die tempo van toediening is gewoonlik 1g/minuut maar moet bepaal word deur die pasiënte se kliniese beeld. Hemopure® kan vinniger toegedien word indien nodig. Verwyder die foelie omhulsel voor gebruik en gebruik dan binne 24 uur. Hemopure® moet asepties toegedien word in 'n sentrale of perifere aar en 'n standaard intraveneuse infuusstel en kateter kan gebruik word. Ander medisyne of oplossings moet nie by die infuussak gevoeg word nie. Die inhoud van meer as een sak moet nie gemeng word nie.

Oorkruis tipering van bloed is nie nodig met die gebruik van Hemopure® nie. Bloedoortappings is nie teenaangedui in pasiënte wat Hemopure® ontvang nie.

Nuwe-effekte en spesiale voorsorgmaatreëls:

Wanneer Hemopure® met kontrole groepe vergelyk word, en die absolute verskil in insidensie vergelyk word, het die volgende nuwe-effekte $\geq 5\%$ voorgekom: abdominale pyn, astenie, laboratoriumtoets abnormaliteite, pyn, hipertensie, geelsug, naarheid, uitslag en hematurie.

Geelsug en hipertensie het aansienlik meer voorgekom in pasiënte wat Hemopure® ontvang het. Geelsug is 'n nuwe-effek wat te wagte kan wees as gevolg van die afbraak van hemoglobien na bilirubien. Dit blyk dat dit nie met lewerdisfunksie verband hou nie. Die gemiddelde toename in sistoliese en diastoliese arteriële bloeddruk met Hemopure® is matig (~ 16 en ~ 11mmHg onderskeidelik).

Kortstondige, lig tot matige geïsoleerde verhogings in ensiemavlakke, gewoonlik aspartaam transaminase alanien transaminase, of lipase, kan voorkom na Hemopure® toediening. Dit hou nie verband met hepatitis of pankreatitis nie.

Kardiovaskulêre insidente soos angina, arteriële trombose, miokardiale iskemie, miokardiale infarksie en kongestiewe hartversaking het voorgekom in < 2% van pasiënte.

Sekere nuwe-effekte kan te wagte wees gedurende sjiurgiese prosedures en het voorgekom in Hemopure® kliniese studies: astenie (moegheid / swakheid), koudkry, edeem, koors, hoofpyn, post-operatiewe insnydende pyn, aritmieë (ook atriale fibrillasie), bradikardie, verminderde bloeddruk, verhoogde bloeddruk, tagikardie, abdominale gas, konstipasie, diarree, ileus, naarheid, braking, hipokalsemie, hipokalemie, hipomagneesemie, verwarring, verminderde verstandelike aktiwiteit, slaaploosheid, basillare gekraak, verminderde, asemhalingsklanke, arteriële onversadiging, hipoksemie, respiratoriese ontoereikendheid, seerkeel, jeuk, uitslag, wond dreinerig, oligurie en hematurie.

Serum en plasma monsters van pasiënte wat Hemopure® ontvang het, sal 'n rooi kleur hê as gevolg van die hemoglobien. Dit kan lei tot 'n toename of afname in die resultate van kliniese laboratorium toetse, afhangend van die tipe analiseerder of reagens wat gebruik word. Indien Hemopure® in die plasma of serum tenwoordig is, kan akkurate lesings van bilirubien of albumien, nie met enige tipe instrument verkry word nie. Die Hitachi kliniese chemiese analiseerder is akkuraat vir die bepaling van elektroliete, bloed ureum stikstof, kreatienkinase, glukose, alanien transaminase en aspartaam transaminase. Die Johnson & Johnson Ekatachem is akkuraat vir die bepaling van elektroliete, bloed ureum stikstof, kreatienkinase, glukose, alanien transaminase en aspartaam transaminase en lipase. Protrombientyd (PT) en geaktiveerde gedeeltelike tromboplastientyd (aPTT) kan akkuraat bepaal word deur metodes wat meganies, magneties en lig verstrooi. In die teenwoordigheid van Hemopure® is optiese metodes nie betroubaar vir koagulase ontledings nie. Daar is geen inmenging met hematologie of urianaliese nie.

Na die infusie van Hemopure® kan pols oksimetriewaardes effens verlaag, as gevolg van die suurstof ewigskurwe wat na regs beweeg, in vergelyking met menslike rooibloedselle. Die arteriële parsiele druk van suurstof word nie beïnvloed deur Hemopure® nie.

Voorsorg moet getref word gedurende die toediening van Hemopure, wat 'n isotoniese kolloïdale oplossing is. Soos met enige kolloïd, moet sirkulasie-oorbelaeding voorkom word. In die kliniese studies, was daar is nie oortuigende bewys van nuwe-effekte in pasiënte met hartversaking nie. Die pasiënte moet egter ondersoek word vir vloeistof oorbelaeding veral gedurende en na die toediening van dosisse groter as 60g per dag. Gesamentlike toediening met ander kolloïde (soos plasma of hetastarch) moet met omsigtigheid benader word.

Die veiligheid van Hemopure® vir meer as een behandelings periode, gedefinieer as minder of gelyk aan ses dae, is nog nie aangetoon nie. Die veiligheid van Hemopure® in swanger en lakterende vroue is nie bewys nie. Die toediening van Hemopure® aan hierdie vroue word nie aanbeveel nie.

Daar is onvoldoende data om die gebruik van Hemopure® in kinders te ondersteun.

Indien 'n skielike hipersensitiwiteitsreaksie plaasvind, moet die toediening van Hemopure® dadelik gestaak word en toepaslike behandeling toegedien word.

Bekende simptome van oordosering en besonderhede van behandeling:

Oordosering of te vinnige toediening van Hemopure®, 'n kolloïd, kan aanleiding gee tot 'n sirkulasie oorbelaeding. Dit manifesteer as pulmonêre edeem en/of perifere edeem. Indien hierdie simptome voorkom, moet die Hemopure® infuus gestaak word en die normale ondersteuningsbehandeling gegee word.

Aanbleding:

250mL (30g) hemoglobien glutameer-250 (bees) 13g/dL in 'n deurskynende infuussak was geseël word in 'n aluminium sak.

Bergingsvoorskrifte:

Berg by 2-30°C in die foelie sak. Moet nie vries nie.

Gebruik binne 24 uur nadat die foelie sak verwyder is.

Moet nie enige medisyne of ander oplossings toevoeg tot die sak nie. Hou buite die bereik van kinders.

Naam en besigheidsadres van applikant:

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Datum van publikasie van hierdie voubiljet:

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