

Blood Substitutes

There are no FDA-approved blood substitutes available for routine use in the US.

Hemopure (HbO2 Therapeutics) is a hemoglobin-based oxygen carrier (HBOC) ready for immediate infusion and may be available for emergency single-patient IND use through the FDA's expanded-access program.

<https://www.hbo2therapeutics.com/all-publications>

Hemopure [hemoglobin glutamer-250(bovine); HBOC-201] is an investigational drug that has not been approved by the FDA as being safe and effective for human use.

<https://www.hbo2therapeutics.com/our-product>

How to procure Hemopure for a patient at UCSF:

1. Provider and Hematology Consult Service verify that patient/surrogate has provided written informed consent for receiving a hemoglobin-based product
2. Hematology Consult Service notifies Pharmacy about plan to procure product
3. Hematology Consult Service contacts manufacturer to confirm that they are willing to supply the product free of charge, and the manufacturer must supply the FDA with a letter of authorization.
4. Hematology Consult Service submits request to the FDA for expanded access to an investigational drug under a single-patient IND.
5. Hematology Consult Service notifies UCSF IRB
6. Product is shipped to the Pharmacy and dispensed by the Pharmacy
7. Note: Transfusion Service (Blood Bank) does not procure/store/dispense this product. All requests should go through the Hematology Consult Service

Submission of eIND: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/physician-request-single-patient-ind-compassionate-or-emergency-use>

Contact information for FDA: <https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information>

Contact Information for Manufacturer:

<https://www.hbo2therapeutics.com/contact>

- Fill out the web form, provide contact information and await phone call from the company.
- Product may be available within 1-2 days

SUMMARY DIRECTIONS FOR USE OF HEMOPURE (HBOC-201):

General description: HBOC-201 (HEMOPURE) is a polymerized bovine hemoglobin solution (average MW 250 kD) in lactated Ringers solution, contains 0.002 moles or 112mg of iron as Fe-protoporphyrin. HBOC-201 is ~ 1 million times smaller than RBC. Each 250 mL bag of HBOC-201 contains ~32g of hemoglobin (Hb), (conc. ~13g/dL of Hb) and has the same O₂ carrying capacity (1.39 mL O₂/g Hb) as whole blood (13-16 g/dl Hb). By comparison, packed red cells (pRBC) have 26-32 g/dL Hb and a much longer half-life than HBOC-201. To date HBOC-201 has been used in ~2000 patients, for various anemia/ischemia indications. HBOC-201 can transport/relinquish O₂ efficiently, scavenges NO and has colloidal properties. HBOC-201 is vasoactive, has pressor-like properties that can cause systemic alterations such as mild to moderate MAP and PAP elevations and plasma volume expansion (very similar to 6% albumin solution).

Product is ready for IV infusion: It does NOT require reconstitution, special lines, or filters. It is stable at room (2-30 °C) temperature for 3 years but MUST NOT BE FROZEN. Once the outer pouch is removed, the product must be used within 24 hours and any unused product must be discarded.

No blood typing or cross-matching with patient's blood is required.

Administration. HBOC-201 can be administered via any intravenous pump. However, a pump is not necessary for administration, but simplifies dosing and continuous infusion (see below). HBOC-201 may be warmed to 37°C prior to administration if necessary. DO NOT warm HBOC-201 in a microwave.

Dosing: infuse the first unit of HBOC-201 over 1 hour (~5mL/min) when Hb less than 5-6 g/dl associated with evidence (ECG, Lactate etc) of ischemia followed by a second unit of HBOC-201 infused over 2 hours. Infusion rates can be slower depending on cardiac status/urgency. With a baseline Hb level of ~5g/dL ~2-3 units/24 hours or use continuous slow infusion of 1 bag per 8-12 hours via e-pump, as indicated clinically.

Blood Pressure: be aware of HBOC-201 pressor-like effect so you may want to reduce or stop use of pressors. Monitor for potential unwanted SBP elevation (≥ 40 mm Hg) and if necessary use Ca channel blockers, sublingual or IV Nitro Glycerin. In preclinical and clinical studies HBOC-201 did not change coronary artery diameter, or volumetric coronary blood flow, coronary vascular resistance or left ventricular stroke work index.

Fluid Balance: Monitor patient's 6 hour fluid balances and if necessary diurese (typically, 20 mg furosemide).

Repeat dosing Hemopure & hematopoiesis is important to maintain therapeutic O₂ carrying benefit HBOC-201 because of 19 hr half-life, with total Hb ≥ 5 g/dl or greater. Recombinant erythropoietin (36,000 units daily), folic acid (5 mg/day), vitamin B12 (1 mg/day for 6 days) and iron (500 mg IV) maximize hematopoiesis.

Hematocrit %: This should be determined from spun pediatric tubemeasurements (rather than values derived by lab instrument estimation from 1/3rd % total Hemoglobin [Hb]). The difference total Hb *minus* hematocrit fraction shows how much patient O₂ delivery depends on HBOC-201.

MetHemoglobin (MetHb). When cellular hemoglobin levels are less than 5 g/d, levels of NADH diaphorase & cytochrome b5 reductase in RBC may be insufficient to prevent some oxidation of Hemopure Hb to MetHb. Should MetHb increase > 10-15%, we recommend use of ascorbic acid (oral or IV) 500 – 1000 mg b.i.d. to minimize MetHb formation during HBOC-201 infusion. Addition of methylene blue maybe also be helpful. In

patients with known or suspected G6PD deficiency, methylene blue should not be used to treat MetHb as it may result in hemolysis and further exacerbate the patient's anemia.

Plasma Volume Distribution. HBOC-201 increases the oxygen content of the blood by increasing the oxygen content of the plasma. Following infusion, the plasma and total hemoglobin concentrations increase but the hematocrit may decrease related to hemodilution as a result of HBOC-201's colloidal properties. Because of the presence of HBOC-201, the plasma/ serum from a patient that has received this product will give the appearance of hemolysis,

Laboratory Testing Interferences. The presence of HBOC-201 in serum may result in artifactual increases or decreases in the results of some serum chemistry tests, depending on the type of analyzer and reagents used. Interferences will occur with measurement of PT and aPTT when optical methods are used. These can be measured accurately using mechanical, magnetic and light scattering techniques. Platelets can also be accurately measured. The red plasma/serum is due to the presence of HBOC-201 and should not be confused with hemolysis of the red blood cells. (Note: hemolysis cannot be detected in the presence of HBOC-201.) HBOC-201 has no clinical effect on coagulation parameters, other than dilution. Colorimetric interferences with serum chemistry tests may occur as long as hemoglobin is present in the serum.

Hemoglobin and hematocrit vs Plasma Hemoglobin. Hematocrit (Hct) measures the percentage volume of red blood cells in the plasma. Hemopure is carried in the plasma. For accurate assessment of the total oxygen carrying ability of the patient's blood, measurement of total hemoglobin concentration = RBC Hb + plasma Hb x (1 - Hct), where Hct is measured as a fraction of total Hb.

Logistics of HBOC-201 Administration. There is no known disease transmission or immune effects; Rheology improves as HBOC-201 is an acellular fluid.

Monitoring and Repeated dosing. Monitor total Hb, not Hct. Repeat dosing needed as $\frac{1}{2}$ life 19-24 hrs. 3 units PRBC were roughly equivalent to 10 units HBOC-201 for surgical bleeding¹

Interferences with bedside pulse oximetry (SpO₂). HBOC-201 interferences occur with bedside SpO₂ monitoring. HBOC-201 has right shifted Hb dissociation curve¹. If RBC [Hb] was half and plasma HBOC Hb was half, SpO₂ monitor would show $(100 + 85)/2 =$ approximately 92-93%. True Hb O₂ saturation can be obtained by co-oximetry.