

## Reconstitution of Panhematin™ with Human Albumin: Instructions for Preparation and Intravenous Infusion

### Background.

Hemin is the preferred treatment for acute porphyric attacks (1) and is available in the United States as lyophilized hematin (Panhematin™, Recordati Rare Diseases). Product labelling approved by the US Food and Drug Administration (FDA) recommends that it be reconstituted with sterile water just before infusion, and then administered through a large arm vein or by central venous catheter to avoid phlebitis. After drug approval in 1983, it was found that hematin is unstable when reconstituted with sterile water, and degradation products formed before infusion bind to endothelial cells, clotting factors and platelets and can cause infusion site phlebitis and a transient coagulopathy.

Many physicians and medical centers have adopted the published method of Bonkovsky and colleagues (2) for reconstituting hematin with 25% human albumin. Each albumin molecule has a single high-affinity heme binding site and additional lower affinity sites. This reconstitution method uses equimolar amounts of albumin and hematin to optimize stability as heme albumin. Although widely used, this is an off-label method (not approved by the FDA). Experience indicates that infusion site phlebitis and coagulopathy are less frequent with this method of reconstitution.

In 2017, Recordati Rare Diseases updated product labelling and increased the amount of hematin in each vial from 313 mg to 350 mg. Because the size of the vial was not increased, this made reconstitution with albumin more difficult. Also, the dose for overweight patients if, as previously recommended, is limited to one vial, would increase from 313 mg to up to 350 mg. Whether this increase in the maximum dose might be a safety concern is not known.

### Method for reconstitution.

Panhematin™ is reconstituted and prepared for infusion in the Pharmacy. How long the stability of hemin is maintained by this method has not been closely studied. Therefore, the Pharmacy should be notified in advance that a dose is needed, but should not reconstitute the dose until it receives word from the clinical unit that a suitable vein has been accessed, normal saline is being infused and the nursing staff is ready to piggyback the heme albumin to the saline infusion line as soon as it is delivered to the unit.

A stable hemin solution is prepared by reconstituting lyophilized hematin with 147 mL of 25% human serum albumin instead of sterile water. This provides for equimolar amounts of hematin and albumin. It is important not to add sterile water instead of albumin at any time because this will immediately lead to degradation products.

Materials needed” 1.) A 350-mg vial of lyophilized hematin, 2.) two 150-mL sterile empty glass bottles for infusion, 3.) three 50-mL vials of 25% albumin (only 147 mL will be used), 4.) a 5-micron filter disc, and 5.) a vent needle.

To prepare the hemin for infusion:

1. Reconstitution of 350 mg of hematin requires 147 mL of 25% albumin. First, reconstitute the vial containing 350 mg vial of lyophilized hematin with 132 mL of 25% albumin. NOTE: ONLY 132 mL of 25% albumin will fit in the vial, so an additional 15 mL is added later. Because 132 mL will almost completely fill the vial, the albumin must be injected into the vial slowly and the vial must be vented. Use a vented needle or make a vent with a separate needle to release the air pressure.
2. *Do not shake the mixture.* Swirl the vial 15 to 20 times to ensure that it is thoroughly mixed (it will be difficult to see if the materials are blended because of the dark color of hemin).
3. After reconstitution, transfer the contents of the vial into a larger sterile, empty glass bottle and then add the additional 15mL of albumin needed. The final hemin concentration in the glass bottle is 2.4 mg/mL. The volume required to deliver the desired dose (usually 3 to 4 mg/kg of body weight) should be calculated according to representative volumes for corresponding body weights (**Table**).

4. Withdraw and filter the full contents of the vial using a 60mL syringe and a 5 micron filter disc. Multiple transfers will be necessary.
5. Inject the dose into a second 150 mL empty sterile bottle.
6. Label the bottle.
7. Place the bottle in an amber bag to protect the mixture from light. Also place a vented spike adapter in the bag. Affix a yellow Medication Administrations Recording blood products label (record both albumin and lyophilized hemein, since both are human blood products) to the amber bag, and then place the amber bag inside a STAT-labeled bag.
8. Hand-deliver the bag to the clinical unit immediately. Once reconstituted with albumin, the drug is considered stable for 1 hour. The heme–albumin complexes may be stable for much longer, but these solutions do not contain bacteriostatic agents and should be infused within about 1 hour of preparation.

### Method for Infusion.

1. Establish venous access. This is done before asking the Pharmacy to prepare the dose. A large peripheral vein, peripherally inserted central catheter, central line, or central port should be used. If none of these is available, a small peripheral vein may be used if infusing well.
2. Start an Infusion of 0.9% sodium chloride at a moderate rate.
3. Ask the Pharmacy to prepare the dose, and once prepared, deliver it to the unit immediately.
4. Start infusing the dose, as soon as possible after it is delivered, as a piggyback to the 0.9% saline that is already infusing. The dose should be infused over a period of at least 60 minutes or at a rate that should not exceed 1 mL/min, which corresponds to the recommendation for infusing 25% human albumin (3, 4). A shorter infusion time may cause some intravascular volume expansion and symptoms such as headache. *An inline filter is not used*, because the dose was just filtered in the Pharmacy. Provide light protection using an amber bag, or a paper bag.
5. Progress with the infusion should be checked by the nursing staff at least every 10-15 minutes to be sure it is proceeding at an appropriate rate. As much as possible of the heme albumin should be infused, and no significant amount left in the bottle or tubing.
6. After the heme–albumin is infused, the infusion of 0.9% saline is continued at a moderate rate for at least 10 minutes to clear the line, needle and vein. If a central line or port was used, this should also be cleared of heme–albumin, which otherwise may precipitate or congeal and occlude the line or port.

### Comments.

Reconstitution of lyophilized hemein with albumin is recommended, particularly when a dose is to be infused into a peripheral vein. Albumin prevents formation of hemein degradation products that bind to endothelial cells, platelets, and coagulation factors. Experience has shown that this method reduces the frequency of phlebitis at infusion sites and helps to prevent progressive loss of venous access in patients with frequent attacks who require repeated hemein infusions. Reconstitution with albumin also prevents transient coagulopathy, which at least on one occasion was associated with bleeding (5). Although coadministration of hemein and albumin is not approved by the U.S. Food and Drug Administration, it offers the advantage of preventing these side effects. Heme arginate, which is available in Europe and South Africa, is more stable after dilution and is less likely to cause phlebitis and coagulopathy (5); however, reconstitution with albumin instead of saline has also been recommended for this product to preserve peripheral veins (6).

The currently recommended regimen for treating acute attacks of porphyria is hemein, 3 to 4 mg/kg, daily for 4 days. Extended treatment is indicated in some cases, particularly if there is advanced neuropathy (1). Most experts in the field believe that daily doses less than 3 mg/kg are probably less effective. Twice-daily administration probably has no advantage over a once daily regimen. A single dose should not exceed 4 mg/kg or the contents of one vial, whichever is less. Single vials previously contained 313 mg and now contains 350 mg. Hemein is initially distributed in plasma and is then taken up primarily in the liver. Because little is distributed in fat or other tissues, a single dose for an obese patient should seldom if ever exceed a single 350 mg vial. No more than 6 mg/kg should be given in a 24-hour period.

A regimen of hemin therapy for prevention of attacks has not been established. Administration of 3 to 4 mg/kg once or twice weekly (7) (or during the premenstrual period for women with frequent episodes that occur in a cyclic pattern) has been effective in some patients.

<b>Table. Representative Volumes of Heme–Albumin Solution Needed To Achieve Desired Hemin Dosage of 4 mg/kg Daily</b>		
<b>Body Weight (kg)</b>	<b>Hemin (mg)</b>	<b>Heme-albumin solution (mL)</b>
50	200	83
60	240	100
70	280	117
80	313	132
87.5	350*	147
* For a single dose, use of more than 1 vial of lyophilized hematin (350 mg) is seldom if ever indicated.		

## References

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