PANHEMATIN - hemin injection, powder, lyophilized, for solution
RECORDATI RARE DISEASES, INC.

Panhematin®
Hemin For Injection

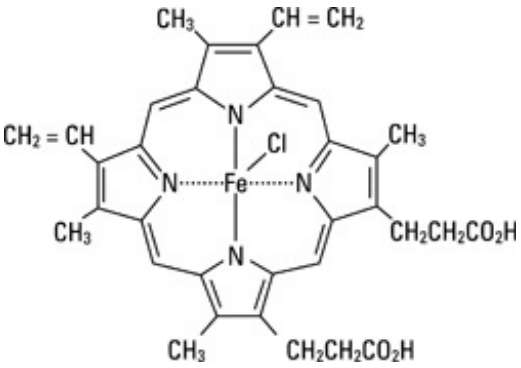
Rx only
For intravenous infusion only.

PANHEMATIN (hemin for injection) should only be used by physicians experienced in the management of porphyrias in hospitals where the recommended clinical and laboratory diagnostic and monitoring techniques are available.

PANHEMATIN therapy should be considered after an appropriate period of alternate therapy (i.e., 400 g glucose/day for 1 to 2 days). (See "WARNINGS", "PRECAUTIONS" and "DOSAGE AND ADMINISTRATION" sections.)

DESCRIPTION

PANHEMATIN (hemin for injection) is an enzyme inhibitor derived from processed red blood cells. Hemin for injection was known previously as hematin. The term hematin has been used to describe the chemical reaction product of hemin and sodium carbonate solution. Hemin is an iron containing metalloporphyrin. Chemically hemin is represented as chloro [7,12-diethenyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(2-)-N^{21},N^{22},N^{23},N^{24}] iron. The structural formula for hemin is:



PANHEMATIN is a sterile, lyophilized powder suitable for intravenous administration after reconstitution. Each dispensing vial of PANHEMATIN contains the equivalent of 313 mg hemin, 215 mg sodium carbonate and 300 mg of sorbitol. The pH may have been adjusted with hydrochloric acid; the product contains no preservatives. When mixed as directed with Sterile Water for Injection, USP, each 43 mL provides the equivalent of approximately 301 mg hematin (7 mg/mL).

CLINICAL PHARMACOLOGY

Heme acts to limit the hepatic and/or marrow synthesis of porphyrin. This action is likely due to the inhibition of δ-aminolevulinic acid synthetase, the enzyme which limits the rate of the porphyrin/heme biosynthetic pathway. The exact mechanism by which hematin produces symptomatic improvement in patients with acute episodes of the hepatic porphyrias has not been elucidated.[1,9]

Following intravenous administration of hematin in non-jaundiced human patients, an increase in fecal urobilinogen can be observed which is roughly proportional to the amount of hematin administered.

This suggests an enterohepatic pathway as at least one route of elimination. Bilirubin metabolites are also excreted in the urine following hematin injections.[2]

PANHEMATIN (hemin for injection) therapy for the acute porphyrias is not curative. After discontinuation of PANHEMATIN treatment, symptoms generally return although in some cases remission is prolonged. Some neurological symptoms have improved weeks to months after therapy although little or no response was noted at the time of treatment.

Other aspects of human pharmacokinetics have not been defined.

INDICATIONS AND USAGE

PANHEMATIN (hemin for injection) is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women.

Manifestations such as pain, hypertension, tachycardia, abnormal mental status and mild to progressive neurologic signs may be controlled in selected patients with this disorder.

Similar findings have been reported in other patients with acute intermittent porphyria, porphyria variegata and hereditary coproporphyria. PANHEMATIN is not indicated in porphyria cutanea tarda.

CONTRAINDICATIONS

PANHEMATIN is contraindicated in patients with known hypersensitivity to this drug.

WARNINGS

PANHEMATIN is made from human blood. Products made from human blood may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening blood donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Recordati Rare Diseases, (1-888-575-8344). The physician should discuss the risks and benefits of this product with the patient.

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

PANHEMATIN therapy is intended to limit the rate of porphyria/heme biosynthesis possibly by inhibiting the enzyme δ-aminolevulinic acid synthetase. For this reason, drugs such as estrogens, barbituric acid derivatives and steroid metabolites which increase the activity of δ-aminolevulinic acid synthetase should be avoided.

Also, because hemin for injection has exhibited transient, mild anticoagulant effects during clinical studies, concurrent anticoagulant therapy should be avoided.[9] The extent and duration of the hypocoagulable state induced by PANHEMATIN has not been established.

PRECAUTIONS

General

Clinical benefit from PANHEMATIN depends on prompt administration. Attacks of porphyria may progress to a point where irreversible neuronal damage has occurred. PANHEMATIN therapy is intended to prevent an attack from reaching the critical stage of neuronal degeneration. PANHEMATIN is not effective in repairing neuronal damage.[9]

Recommended dosage guidelines should be strictly followed. Reversible renal shutdown has been observed in a case where an excessive hematin dose (12.2 mg/kg) was administered in a single infusion. Oliguria and increased nitrogen retention occurred although the patient remained asymptomatic.[4] No worsening of renal function has been seen with administration of recommended dosages of hematin.[9]

A large arm vein or a central venous catheter should be utilized for the administration of PANHEMATIN to avoid the possibility of phlebitis.

Since reconstituted PANHEMATIN is not transparent, any undissolved particulate matter is difficult to see when inspected visually. Therefore, terminal filtration through a sterile 0.45 micron or smaller filter is recommended.

Because increased levels of iron and serum ferritin have been reported in post-marketing experience, physicians should monitor iron and serum ferritin in patients receiving multiple administrations of PANHEMATIN (See "ADVERSE REACTIONS" section).

Tests for Diagnosis and Monitoring of Therapy

Before PANHEMATIN therapy is begun, the presence of acute porphyria must be diagnosed using the following criteria:[9]

a. Presence of clinical symptoms.
b. Positive Watson-Schwartz or Hoesch test. (A negative Watson-Schwartz or Hoesch test indicates a porphyric attack is highly unlikely. When in doubt quantitative measures of δ-aminolevulinic acid and porphobilinogen in serum or urine may aid in diagnosis.)

Urinary concentrations of the following compounds may be *monitored* during PANHEMATIN therapy. Drug effect will be demonstrated by a decrease in one or more of the following compounds.[3-6]

ALA - δ-aminolevulinic acid
UPG - uroporphyrinogen
PBG - porphobilinogen
coproporphyrin

Carcinogenesis, Mutagenesis, Impairment of Fertility

PANHEMATIN was not mutagenic in bacteria systems *in vitro* and was not clastogenic in mammalian systems *in vitro* and *in vivo*. No data are available on potential for carcinogenicity or impairment of fertility in animals or humans.

Pregnancy

Teratogenic effects-Pregnancy Category C: Animal reproduction studies have not been conducted with hematin. It is also not known whether hematin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. For this reason PANHEMATIN should not be given to a pregnant woman unless the expected benefits are sufficiently important to the health and welfare of the patient to outweigh the unknown hazard to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PANHEMATIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 16 years of age have not been established.

Geriatric Use

Clinical studies in PANHEMATIN did not include sufficient numbers of subjects aged 65 and over to

determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trials Experience

Phlebitis with or without leucocytosis and with or without mild pyrexia has occurred after administration of hematin through small arm veins.

Post-marketing Experience

Reversible renal shutdown has occurred with administration of excessive doses (See "PRECAUTIONS" section).

There have been post-marketing literature reports of thrombocytopenia and coagulopathy (including prolonged prothrombin time and prolonged partial thromboplastin time) in patients receiving PANHEMATIN.[8] Iron overload and serum ferritin increased have also been reported (See "PRECAUTIONS" section).

To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases at 1-888-575-8344 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Reversible renal shutdown has been observed in a case where an excessive hematin dose (12.2 mg/kg) was administered in a single infusion. Treatment of this case consisted of ethacrynic acid and mannitol.[7]

DOSAGE AND ADMINISTRATION

Before administering PANHEMATIN, an appropriate period of alternate therapy (i.e., 400 g glucose/day for 1 to 2 days) must be considered. If improvement is unsatisfactory for the treatment of acute attacks of porphyria, an intravenous infusion of PANHEMATIN containing a dose of 1 to 4 mg/kg/day of hematin should be given over a period of 10 to 15 minutes for 3 to 14 days based on the clinical signs. In more severe cases this dose may be repeated no earlier than every 12 hours. No more than 6 mg/kg of hematin should be given in any 24 hour period.

After reconstitution each mL of PANHEMATIN contains the equivalent of approximately 7 mg of hematin. The drug may be administered directly from the vial.

Dosage Calculation Table
1 mg hematin equivalent = 0.14 mL PANHEMATIN
2 mg hematin equivalent = 0.28 mL PANHEMATIN
3 mg hematin equivalent = 0.42 mL PANHEMATIN
4 mg hematin equivalent = 0.56 mL PANHEMATIN

Since reconstituted PANHEMATIN is not transparent, any undissolved particulate matter is difficult to see when inspected visually. Therefore, terminal filtration through a sterile 0.45 micron or smaller filter is recommended.

Preparation of Solution:

Reconstitute PANHEMATIN by aseptically adding 43 mL of Sterile Water for Injection, USP, to the dispensing vial. Immediately after adding diluent, the product should be shaken well for a period of 2 to 3 minutes to aid dissolution.

NOTE: Because PANHEMATIN contains no preservative and because PANHEMATIN undergoes rapid chemical decomposition in solution, it should not be reconstituted until immediately before use. After the first withdrawal from the vial, any solution remaining must be discarded.

No drug or chemical agent should be added to a PANHEMATIN fluid admixture unless its effect on the chemical and physical stability has first been determined.

HOW SUPPLIED

PANHEMATIN is supplied as a sterile, lyophilized black powder in single dose dispensing vials (NDC 55292-701-54) in a carton (NDC 55292-701-55). When mixed as directed with Sterile Water for Injection, USP, each 43 mL provides the equivalent of approximately 301 mg hematin (7 mg/mL). Store lyophilized powder at 20-25°C (68-77°F). See USP controlled room temperature.

Caution: The packaging (vial stopper) of this product contains natural rubber latex which may cause allergic reactions.

REFERENCES

1. Bickers, D., Treatment of the Porphyrias: Mechanisms of Action, J Invest Dermatol 77(1):107-113, 1981.
2. Watson, C. J., Hematin and Porphyria, editorial, N Engl J Med 293(12): 605-607, September 18, 1975.
3. Lamon, J. M., Hematin Therapy for Acute Porphyria, Medicine 58(3): 252-269, 1979.
4. Dhar, G J., et al., Effects of Hematin in Hepatic Porphyria, Ann Intern Med 83: 20-30, 1975.
5. Watson, C. J., et al., Use of Hematin in the Acute Attack of the “Inducible” Hepatic Porphyrias, Adv Intern Med 23: 265-286, 1978.
6. McColl, K. E., et al., Treatment with Haematin in Acute Hepatic Porphyria, Q J Med, New Series L (198): 161-174, Spring, 1981.
7. Dhar, G. J., et al., Transitory Renal Failure Following Rapid Administration of a Relatively Large Amount of Hematin in a Patient with Acute Intermittent Porphyria in Clinical Remission, Acta Med Scand 203: 437-443, 1978.
8. Morris, D.L., et al., Coagulopathy Associated with Hematin Treatment for Acute Intermittent Porphyria, Ann Intern Med 95: 700-701, 1981.
9. Pierach, C. A., Hematin Therapy for the Porphyric Attack, Semin Liver Dis 2(2): 125-131, May, 1982.

Manufactured by: Fresenius Kabi USA, LLC
Raleigh, NC 27616

For: Recordati Rare Diseases Inc.
Lebanon, NJ 08833, U.S.A.
U.S. Lic. No. 1899

RECORDATI RARE DISEASES GROUP

Revised: February 2013

750-04243-7

PRINCIPAL DISPLAY PANEL

NDC 55292-701-54

Single Dose Vial

Hemin For Injection Panhematin®

313 mg Hemin per Vial

For Intravenous Infusion Only Sterile Powder for Injection

RECORDATI RARE DISEASES GROUP

Rx only

Each vial contains:
Hemin ..... 313 mg
Sodium Carbonate ..... 215 mg
Sorbitol ..... 300 mg
pH may have been adjusted with hydrochloric acid.

Contains no preservatives.

When mixed as directed, each 43 mL provides the equivalent of approximately 301 mg hematin (7 mg/mL).

See package insert for full prescribing information and appropriate caution statements regarding administration.

Caution: Vial stopper contains latex.

The patient and physician should discuss the risks and benefits of this product.

Store powder at 20-25°C (68-77°F).
See USP controlled room temperature.

DIRECTIONS FOR MIXING:
Add 43 mL of Sterile Water for Injection, USP. Shake to aid dissolution. Infusion may be given from this vial.

USE IMMEDIATELY AFTER MIXING.
Discard any unused portion.

Mfd. by: Fresenius Kabi USA, LLC
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780-04245-4

Lot:

Exp.:

NDC 55292-701-55

Contains One Vial

Hemin For Injection Panhematin®

313 mg Hemin per Vial

For Intravenous Infusion Only Sterile Powder for Injection

RECORDATI RARE DISEASES GROUP

Rx only

Each vial contains:
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® Trademark of Recordati Rare Diseases Inc.

Lot No.

Exp. Date

Store powder at 20-25°C (68-77°F).
See USP controlled room temperature.

Mixing directions:
1. Prep stopper.
2. Insert vent needle in “air” target.
3. Add 43 mL of Sterile Water for Injection, USP.
4. Immediately after adding diluent shake to aid dissolution.
5. May be administered directly from original single dose dispensing vial.
6. Administer by intermittent intravenous infusion over a period of from 10 to 15 minutes.

USE IMMEDIATELY AFTER MIXING.
Discard any unused portion.

See package insert for full prescribing information and appropriate caution statements regarding administration.

Caution: Vial stopper contains latex.

The patient and physician should discuss the risks and benefits of this product.

PANHEMATIN

hemin injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55292-701
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Hemin (UNII: 743LRP9S7N) (Hemin - UNII:743LRP9S7N)	Hemin	7 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Sodium Carbonate (UNII: 45P3261C7T)	
Sorbitol (UNII: 506T60A25R)	
Hydrochloric Acid (UNII: QTT17582CB)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55292-701-55	1 in 1 CARTON	07/20/1983	01/24/2020
1	NDC:55292-701-54	43 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA101246	07/20/1983	01/24/2020

Labeler - RECORDATI RARE DISEASES, INC. (181699406)

Establishment

Name	Address	ID/FEI	Business Operations
Xellia Pharmaceuticals USA, LLC		079459964	MANUFACTURE(55292-701)

Revised: 6/2017 RECORDATI RARE DISEASES, INC.