PANHEMATIN®
(HEMIN FOR INJECTION)

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Help treat **recurrent** attacks of AIP

Indication:[1]

PrPANHEMATIN® (hemin for injection) is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.

Limitations of Use:

- Before administering PANHEMATIN, consider an appropriate period of carbohydrate loading (i.e., 400 g glucose/day for 1 to 2 days).
- 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.

AIP = Acute intermittent porphyria

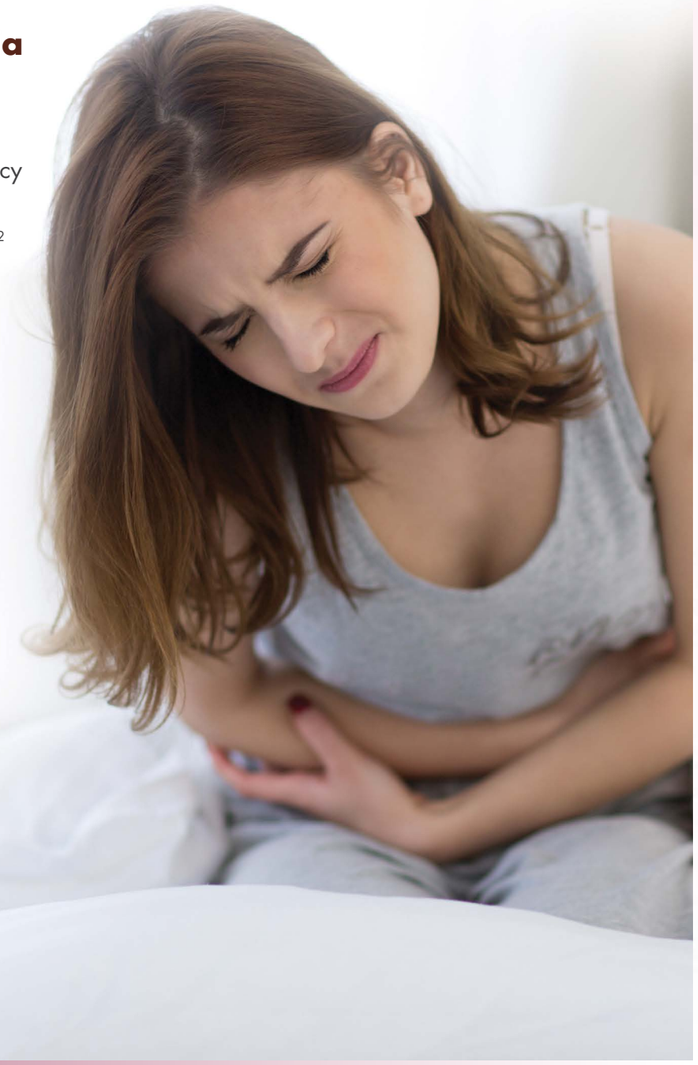
What is PANHEMATIN?

PANHEMATIN (hemin for injection) is an enzyme inhibitor derived from processed red blood cells† and is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.

Acute intermittent porphyria defined

Acute intermittent porphyria (AIP) is a rare inherited disease caused by a partial deficiency of the enzyme porphobilinogen (PBG) deaminase in the heme biosynthetic pathway.[2]

- PBG deficiency disrupts normal heme production, which leads to overproduction of porphyrin precursors.[3]
- Abdominal pain, the most common symptom, is usually severe, unremitting, and diffuse.[2]



† Clinical significance unknown.

How does PANHEMATIN work?

The exact mechanism by which hematin produces symptomatic improvement in patients with acute episodes of the hepatic porphyrias has not been elucidated.[1,‡]

- Heme acts to limit the hepatic and/or marrow synthesis of porphyrin. This action is likely due to the inhibition of δ-aminolevulinic acid synthase, the enzyme which limits the rate of the porphyrin/heme biosynthetic pathway.
- PANHEMATIN therapy is intended to limit the rate of porphyria/heme biosynthesis possibly by inhibiting ALA synthase, which is the first enzyme in the heme biosynthetic pathway.

‡ PANHEMATIN is only indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.

How should the presence of AIP be diagnosed before starting PANHEMATIN therapy?

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

1. Presence of clinical symptoms suggestive of acute porphyric attack.
2. Quantitative measurement of porphobilinogen (PBG) in urine. The single-void urine sample should be refrigerated or frozen without additives and shielded from light for subsequent quantitative δ-aminolevulinic acid (ALA), PBG, and total porphyrin determinations. (Note: the classical Watson-Schwartz or Hoesch tests are considered to be less reliable).

PANHEMATIN summary of chemical and clinical response

Chemical and clinical response to the treatment of AIP attacks was assessed in 72 patients.[1,II]

Summary of clinical and chemical response data from PANHEMATIN open-label studies[1]

Investigator/ Publication	AIP patients	Treatment courses	Dose	Other treatments prior to PANHEMATIN	Chemical response†	Clinical response†
Watson CJ et al[1,5]	11	13	4 mg/kg/day or 4 mg/kg 2x/day‡	Glucose	58% to 100% reduction in serum ALA & PBG levels (11/11 patients)	**91%** (10/11 patients)
Pierach CA et al[1,6]	43	82	2-4 mg/kg/day	—— §	For those patients with elevated urinary ALA & PBG levels prior to treatment	**90%** (74/82 treatment courses)
Lamon JM et al[1,7]	11	20	~2-4 mg/kg/day or 2-4 mg/kg 2x/day‡	High carbohydrate intake	Significant reductions in ALA and/or PBG levels ($p<0.001$ to 0.05) (11/11 patients)	**70%** (14/20 treatment courses)
McColl KE et al[1,8]	7	12	4 mg/kg/day or 4 mg/kg 2x/day‡	—— §	50% reduction in urinary ALA and PBG levels from pre-treatment values (7/7 patients)	**58%** (7/12 treatment courses)
Lamon et al[1,9,II]	7	11	1 mg/kg every 24 hours for 3 to 13 days	250-300 g/24 h carbohydrate diet	Decrease in ALA and PBG occurred in every patient (except one PBG value in one patient) when treatment lasted 5 days or longer ($p<0.001$)	——

† Chemical and clinical responses were individually defined by each investigator in each study.

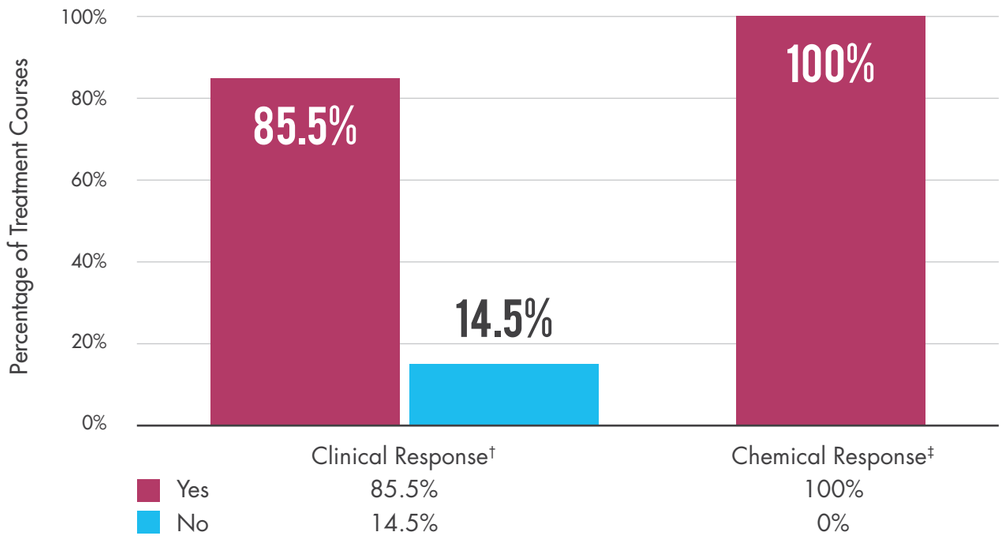
‡ The dose of PANHEMATIN is 0.8 to 3.1 mg/kg/day of hematin for 3 to 14 days based on the clinical signs. The standard dose in clinical practice is 2.3 to 3.1 mg/kg/day. In more severe cases this dose may be repeated no earlier than every 12 hours. Do not exceed 4.6 mg/kg of hematin in any 24 hour period.

§ PANHEMATIN is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.

II Clinical response in Lamon et al (1977) was not evaluated.

PANHEMATIN efficacy data from 5 open-label studies

Patients experienced a clinical response† in 85.5% (141/165) of treatment courses (open label trials).[1]



† Clinical response defined as improvement of symptoms and reduction in pain.
‡ Chemical response defined as normalization of urinary aminolevulinic acid (ALA) and porphobilinogen (PBG).

Additional PANHEMATIN studies[1]

Study	Number of patients treated	Clinical response
Compassionate use, multi-centre, open-label non-comparative study[1,10]	111‖	**73%** (81/111) of patients achieved clinical response for all acute attacks§ **85%** (94/111) of patients had ≥1 clinical response, and 15% (17/111) had no response§
Observational study with patient-reported outcomes[1,11]	90	**55%** (50/90) reported receiving hemin during acute attacks Of these patients, **74%** (37/50) reported PANHEMATIN as being very successful in treatment of abdominal pain and other symptoms. Hemin therapy effectiveness was assessed along with glucose infusions, high carbohydrate diets, and pain medications on a scale from zero being least effective to 10 highly effective. Hemin infusions received a 7.9, glucose infusions a 4.4 (p=0.0781), high carbohydrate diets a 4.7 (p=0.0021), and pain medications a 4.2 (p=0.0049).

§ Clinical response was achieved if the physician determined that the admitting symptoms were resolved, there was a clinically acceptable response, or the patient went into remission.

‖ 90 patients were treated for acute attacks and 21 patients for both acute attacks and prophylaxis. PANHEMATIN is not indicated for prophylaxis.

PANHEMATIN dosing and administration

Dosing considerations[1]

- PANHEMATIN should only be used by or in consultation with physicians experienced in the management of porphyrias.
- Before PANHEMATIN therapy is begun, the presence of acute porphyria must be diagnosed using the following criteria:
  1. Presence of clinical symptoms suggestive of acute porphyric attack.
  2. Quantitative measurement of porphobilinogen (PBG) in urine. The single-void urine sample should be refrigerated or frozen without additives and shielded from light for subsequent quantitative δ-aminolevulinic acid (ALA), PBG, and total porphyrin determinations. (Note: the classical Watson-Schwartz or Hoesch tests are considered to be less reliable).
- Clinical benefit from PANHEMATIN depends on prompt administration. For mild porphyric attacks (mild pain, no vomiting, no paralysis, no hyponatremia, no seizures), a trial of glucose therapy is recommended while awaiting hemin treatment or if hemin is unavailable. For moderate to severe attacks, immediate hemin treatment is recommended. Symptoms of severe attacks are severe or prolonged pain, persistent vomiting, hyponatremia, convulsion, psychosis, and neuropathy. In addition to treatment with PANHEMATIN, consider other necessary measures such as the elimination of triggering factors.
- Monitor urinary concentrations of the following compounds during PANHEMATIN therapy. Effectiveness is demonstrated by a decrease in one or more of the following compounds:

  ALA - δ-aminolevulinic acid,
  PBG - porphobilinogen,
  Uroporphyrin,
  Coproporphyrin

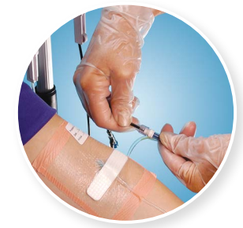
Recommended dose and dosage adjustment[1]

- The dose of PANHEMATIN is 0.8 to 3.1 mg/kg/day of hematin for 3 to 14 days based on the clinical signs.
- The standard dose in clinical practice is 2.3 to 3.1 mg/kg/day.
- In more severe cases this dose may be repeated no earlier than every 12 hours.
- Do not exceed 4.6 mg/kg of hematin in any 24 hour period.

After reconstitution each mL of PANHEMATIN contains the equivalent of approximately 5.4 mg of hematin.

Dosage Calculation Table
1 mg hematin equivalent = 0.18 mL PANHEMATIN
2 mg hematin equivalent = 0.37 mL PANHEMATIN
3 mg hematin equivalent = 0.55 mL PANHEMATIN
4 mg hematin equivalent = 0.74 mL PANHEMATIN

Administration[1]



- For intravenous infusion only.
- PANHEMATIN may be administered directly from the vial. After the first withdrawal from the vial, discard any solution remaining.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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.
- Infuse the dose over a period of at least 30 minutes via a separate line.
- After the infusion, flush the vein with 100 mL of 0.9% NaCl.

Reconstitution[1]

Parenteral Products: Reconstitute PANHEMATIN by aseptically adding 48 mL of Sterile Water for Injection, USP, to the dispensing vial. Shake the vial well for a period of 2 to 3 minutes to aid dissolution.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
268 mg	48 mL	48 mL	5.4 mg/mL

- When mixed as directed with Sterile Water for Injection, USP, each 48 mL provides the equivalent of approximately 261 mg hematin (5.4 mg/mL).
- Because PANHEMATIN contains no preservative and undergoes rapid chemical decomposition in solution, it must be reconstituted immediately before use.
- Do not add other drug or chemical agent to a PANHEMATIN fluid admixture.

PANHEMATIN has an established safety profile

Adverse Reactions in >1% of Patients Treated with PANHEMATIN[1]

The safety profile of PANHEMATIN use was evaluated in a compassionate use study. A total of 130 patients were treated with hemin for acute attacks, prophylaxis, or both.[1,†]

System Organ Class Preferred Term	Adverse Events N (% of Total Adverse Events)	
Description	Total	Possibly or Probably Related to Treatment
Infections and infestations		
Cellulitis	3 (1.5%)	2 (1.0%)
Nervous System Disorders		
Headache	18 (9.2%)	5 (2.6%)
Vascular Disorders		
Phlebitis / Injection site phlebitis	7 (3.6%)	6 (3.1%)
Skin and subcutaneous tissue disorders		
Rash	3 (1.5%)	3 (1.5%)
General Disorders and Administration Site Conditions		
Pyrexia	9 (4.6%)	6 (3.1%)
Catheter-related Complication	7 (3.6%)	3 (1.5%)

Note: In this study, the actual content of drug in the supplied vials ranged from 64.4% to 88.2% of the labelled content. Therefore, the actual amount of drug given to the patients was less than the calculated dose.

† PANHEMATIN is not indicated for prophylaxis. PANHEMATIN is not indicated for males.

Clinical use which has not been discussed elsewhere in this piece:

Pediatrics (< 16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of PANHEMATIN in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age): Clinical data for subjects aged 65 and over was not sufficient to determine whether they respond differently from younger subjects. 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.

Contraindications:

PANHEMATIN is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Relevant warnings and precautions:

- Do not use in patients with known hypersensitivity to PANHEMATIN.
- Risk of phlebitis.
- Risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jacob disease (vCJD) agent, and theoretically the Creutzfeldt-Jacob disease (CJD) agent.
- Transient, mild anticoagulant effects may occur. Avoid concurrent anticoagulant therapy.
- Elevated iron and serum ferritin may occur. Monitor iron and serum ferritin in patients receiving multiple administrations of PANHEMATIN.
- Reversible renal shutdown has been observed in a case where an excessive hematin dose (12.2 mg/kg) was administered in a single infusion. Recommended dosage guidelines should be strictly followed.
- Should be given to a pregnant woman only if clearly needed. Avoid administering hematin in severe pre-eclampsia.
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PANHEMATIN and any potential adverse effects on the breastfed child from PANHEMATIN or from the underlying maternal condition.
- Avoid CYP inducing drugs (such as estrogens, barbituric acid derivatives and steroid metabolites) while on PANHEMATIN therapy.

For more information:

Please consult the Product Monograph at https://www.recordatirarediseases.com/sites/www.recordatirarediseases.com/files/inline-files/panhematin-product-monograph-ENG.pdf for important information related to adverse reactions, interactions and dosing information which has not been discussed in this document.

The Product Monograph is also available by calling McKesson Specialized Distribution at **1-877-827-1306** or email customersupport@gmdpharma.ca.

Help treat recurrent attacks of AIP

- PANHEMATIN is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.
  - Limitations of use: PANHEMATIN therapy is intended to prevent an attack from reaching the critical stage of neuronal degeneration. PANHEMATIN is not effective in repairing neuronal damage.
- Clinical benefit from PANHEMATIN depends on prompt administration.
  - For mild porphyric attacks, a trial of glucose therapy is recommended while awaiting hemin treatment or if hemin is unavailable.
  - For moderate to severe attacks, immediate hemin treatment is recommended. In addition to treatment with PANHEMATIN, consider other necessary measures such as elimination of triggering factors.
- Patients experienced a clinical response in 85.5% of treatment courses based on 5 open-label studies.
  - Clinical response defined by improvement of symptoms and reduction in pain.
- All patients in 5 open-label trials achieved a chemical response to PANHEMATIN therapy.
  - Chemical response defined as normalization of urinary ALA and PBG.
- An established safety profile.

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