Living with

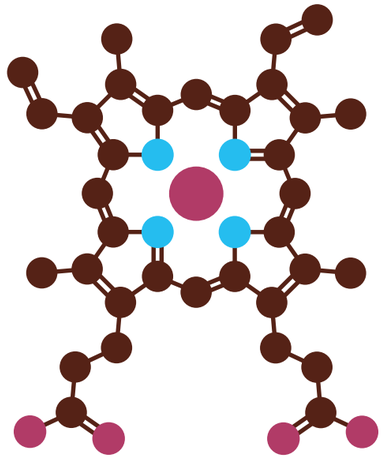
Acute Intermittent Porphyria (AIP)

This brochure will help you understand what **AIP** is, how it affects your body, and how you can help manage your condition.

Contents

What is **AIP**?

AIP is caused by the partial lack of an **enzyme** in the body called **porphobilinogen deaminase (PBGD)**. Enzymes are proteins that carry out chemical reactions in the body. PBGD helps to make heme, which is a molecule that carries oxygen through the bloodstream and throughout the body. The production of heme involves a number of steps. If your body does not have enough PBGD activity, this process is interrupted and heme production gets backed up. This can cause other molecules to build up that are harmful to the body. And when that happens, symptoms of AIP may occur. These are called **AIP attacks**. Symptoms are **intermittent**, meaning they may occur for a set period of time, then go away – only to return later.

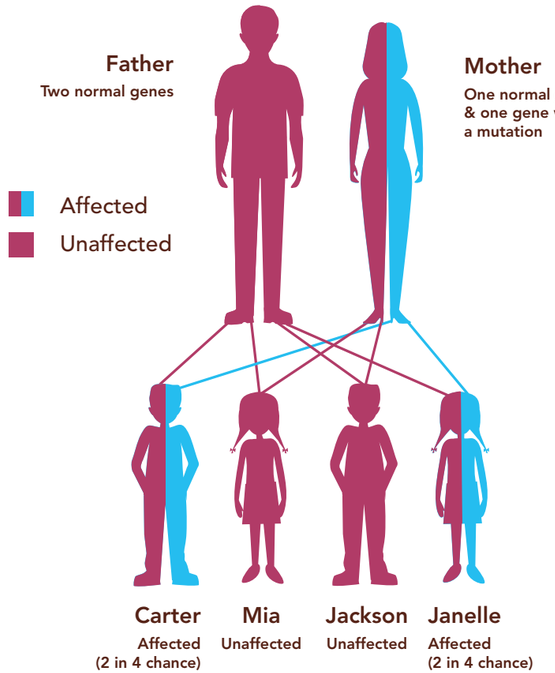


Heme molecule

How does someone get **AIP**?

AIP is a genetic disorder, which is another way of saying that the condition is inherited from one or both parents. If you have AIP, you inherited a hydroxymethylbilane synthase *(HMBS)* gene with a porphyria-causing mutation from one parent and an *HMBS* gene with no mutations from the other parent. The medical term for this kind of inheritance is **autosomal dominant**. Very rarely, someone has an *HMBS* gene mutation and neither parent does.

The job of the *HMBS* gene is to make an enzyme known as hydroxymethylbilane synthase (HMBS). Another name for this enzyme is porphobilinogen deaminase (PBGD).



- In the family shown in the diagram, the father has two normal *HMBS* genes, and the mother has one normal *HMBS* gene and one gene with a mutation. She may or may not have symptoms.
- Each child in the family has a 50% chance of inheriting the gene with a mutation from their mother.
- In this family, Carter and Janelle inherited a gene with a mutation from their mother.
- Individuals with an *HMBS* gene mutation can pass it on to the next generation.

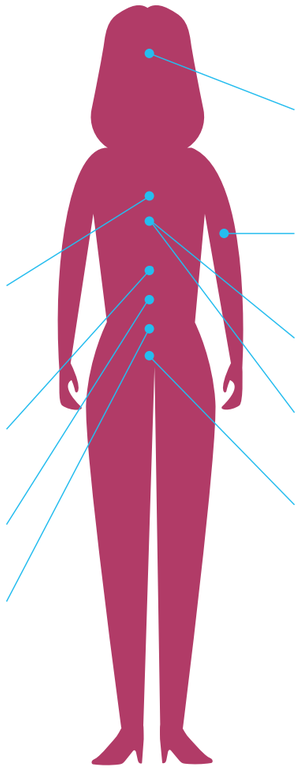
However, even if you inherit a gene mutation, you may not have symptoms of AIP. In fact, **most people with a gene mutation never have symptoms.** And if you do have a gene mutation, it is not possible to predict whether or not you will ever have symptoms, or how severe those symptoms may be.

Doctors may use these terms:

- **Overt AIP:** Someone who currently has symptoms or has had symptoms in the past
- **Latent AIP:** Someone who has never had symptoms but who is at risk for developing symptoms because they have a porphyria-causing mutation in the *HMBS* gene.

What symptoms may be caused by **AIP**?

It's important that you become familiar with symptoms of an AIP attack and that you call your doctor right away if you begin to have symptoms. If not treated right away, AIP attacks can cause serious, long-term health problems or in rare cases be life-threatening. Common symptoms of AIP attacks may include:



Mental health symptoms, such as feeling anxious, restless, or confused

Muscle weakness that usually begins in the arms and often in the shoulders

Fast heart rate

High blood pressure

Dark or reddish urine after the urine has been exposed to air and light

Pain in the arms, legs, chest, neck, or head; the pain may start in the chest or back and move to the abdomen

Nausea or vomiting, commonly along with abdominal pain

Severe pain in the abdomen

Constipation, possibly along with loss of bladder control

Warning symptoms

Some people also have symptoms that occur hours or even a few days before an AIP attack. These warning symptoms may include:

- Pain that is not abdominal pain
- "Brain fog" or feeling mentally cloudy, confused, or unfocused
- Irritability
- Extreme tiredness
- Anxiety and/or agitation
- Headache
- Insomnia or trouble sleeping

Keep a log of your warning symptoms and consider contacting your doctor if you are anticipating an AIP attack.

Chronic symptoms

Some people may have chronic symptoms between AIP attacks, or symptoms that happen occasionally or as often as every day. These symptoms are generally less severe than those that occur during AIP attacks, with pain described as soreness, dullness, aching, throbbing, or burning. Chronic symptoms may include:

- Pain in the abdomen or other parts of the body
- Symptoms involving mental health or mood, such as tiredness, trouble sleeping, and anxiety
- Gastrointestinal (GI) symptoms such as nausea
- Tingling, numbness, or loss of feeling
- Muscle pain

What is unique about the symptoms of **AIP** attacks?

The symptoms that occur during AIP attacks are common in many other diseases. This is one reason why AIP may be misdiagnosed. But there are certain things that may increase suspicion of AIP:

- Pain may be spread throughout the body rather than in focused areas.
- The pain tends to begin gradually and become worse, and it may last for hours or days.
- Pain medicines such as ibuprofen or acetaminophen usually don't help much to relieve the pain caused by AIP attacks. This is because the pain is **neuropathic**, meaning it is caused by nerves.
- You may have one or more symptoms during an AIP attack, but you may not have all of the symptoms that are common during attacks.
- Symptoms of AIP can come and go, and each new attack may be similar to or different from previous attacks.
- Symptoms are often caused by triggers, such as taking certain medicines or dieting to lose weight.

The pain caused by AIP attacks has been described by some people living with AIP as the worst imaginable level of pain:

- **"It's like digesting huge, hot rocks with bone-crushing pain." – L.C.V.**
- **"My insides feel like they're on fire!" – N.T.M.**

What situations may trigger **AIP** attacks?

People with an AIP-causing gene mutation have about half the normal amount of PBGD enzyme activity in their bodies. This is usually enough to produce the amount of heme that the body needs. But certain situations may add stress to this process, causing heme production to get backed up and an attack to become more likely. These situations, or triggers, may include:

- Monthly hormone fluctuations; symptoms are more common during the two weeks before a menstrual period starts
- Weight loss, fasting, or being on a low-carbohydrate diet or ketogenic (keto) diet
- Taking certain medicines, including some types of oral contraceptives, steroids, sedatives, antibiotics, and anti-seizure drugs
- Starting new medicines
- Smoking cigarettes
- Drinking alcohol
- Using illegal drugs
- Stress on the body caused by infections, illness, or surgery

AIP attacks are usually due to several triggers occurring at the same time.

If you have an AIP attack

If you have an AIP attack, you should call your doctor right away. This is very important because if AIP attacks are not treated promptly, they may progress to the point where they cause irreversible nerve damage or even death.

How is **AIP** diagnosed?

It's very important to get properly tested for AIP. Your doctor can order a series of tests to determine whether or not you have AIP:

- **Porphobilinogen (PBG) urine test** – If your doctor suspects AIP, your first test will be a PBG urine test. PBG is one type of molecule that builds up when heme production is disrupted during an AIP attack. During an AIP attack, the level of PBG in urine is much higher than normal. A PBG urine test must be done at or near the time of symptoms to capture a higher PBG level.
- **Follow-up tests** – If the PBG level in your urine is high, more lab tests will show whether you have AIP or another type of acute porphyria.
- **Genetic test** – A DNA test done by a laboratory with specific expertise can identify whether you have a gene that may cause AIP.

Getting an accurate diagnosis is the first step toward managing your attacks of AIP, which is vital for your health.

If a DNA test indicates that you have an *HMBS* gene mutation, your relatives may also want to learn if they have a gene mutation and are at risk of developing symptoms.

What heathcare providers may be involved in your care?

Many people with AIP see a local hematologist who manages their care. A hematologist is a doctor who specializes in diseases of the blood.

It's very important to establish **good relationships with the doctor who is treating your AIP and with nurses and other staff who may be involved in your care.** Mutual trust and respect are important in these relationships. Ideally, you should be in an environment where you are encouraged to ask questions and discuss your treatment.

The American Porphyria Foundation (APF) keeps a list of **porphyria experts** who are experienced in diagnosing and treating porphyrias, including AIP. You can contact the APF to find an expert in your area. Ideally, a doctor who is knowledgeable about AIP will be involved in diagnosing your condition and overseeing your care.

What treatments may be helpful for **AIP** attacks?

Your doctor will determine the best course of treatment. The goal is to reduce the build-up of harmful chemicals and restore balance to the process of heme production.

PANHEMATIN® (hemin for injection)

For a **mild attack**, your doctor will first consider trying carbohydrates in the form of glucose. If your doctor suspects or confirms this therapy is not working, he or she may start PANHEMATIN therapy. For a **moderate to severe attack**, your doctor may begin PANHEMATIN treatment right away. The faster the treatment is started, the better the outcome. Both glucose and PANHEMATIN are given through IV infusions. Infusions can be done on an inpatient basis at a hospital or on an outpatient basis at an infusion center or doctor's office. Your doctor can contact the pharmacist at his or her facility to order PANHEMATIN.

Other Therapies

Your doctor may also prescribe other therapies to:

- Correct any electrolyte imbalances (electrolytes are certain salts and minerals that control the balance of fluids in your body)
- Reduce pain
- Prevent other symptoms

If you have recurrent attacks before menstrual periods, your doctor may recommend a medicine to reduce the production of certain hormones.

Panhematin® (hemin for injection) Indications and Usage

PANHEMATIN is a hemin for injection prescription medication used to relieve repeated attacks of acute intermittent porphyria related to the menstrual cycle in affected women, after initial carbohydrate therapy is known or suspected to be inadequate.

Limitations of Use

- Before giving PANHEMATIN, consider an appropriate trial of carbohydrates [i.e., 400 grams of glucose (a carbohydrate or sugar) per day for 1 to 2 days].
- Attacks of porphyria may progress to a point where irreversible nerve damage has occurred. PANHEMATIN therapy is intended to prevent an attack from reaching the critical stage of nerve breakdown. PANHEMATIN is not effective in repairing nerve damage that has already occurred.

Important Safety Information

- PANHEMATIN is not for patients known to be allergic to this drug.
- Vein inflammation is possible. Use a large arm vein or a central line to administer PANHEMATIN to minimize the possibility of vein inflammation.
- Elevated iron levels may occur. Your doctor must monitor your iron levels if you receive multiple courses of PANHEMATIN.
- PANHEMATIN has a passing and mild blood thinning effect. Avoid blood thinners during PANHEMATIN therapy.
- Reversible kidney shutdown has occurred when too high a dose of PANHEMATIN was given in a single dose.
- PANHEMATIN may carry a risk of transmitting agents that can cause infections, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- Most common side effects are headache, fever, infusion site reactions, and vein inflammation.
- **To report SUSPECTED SIDE EFFECTS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
- When taking PANHEMATIN, do not take drugs such as estrogens (e.g., oral contraceptives), barbiturates (drugs that help with sleep and used to treat epilepsy) or steroids (body hormone-like drugs), because such drugs can trigger an attack or make an attack worse.

Please see accompanying Full Prescribing Information.

How can you meet the challenges caused by **AIP**?

If you have overt AIP, there are many things you can do on your own and with others to stay healthy and prepare for the challenges caused by AIP.

Your doctor can help you develop two different plans: an everyday plan and an emergency plan.

Develop an everyday plan

The goal of your everyday plan will be to stay healthy and prevent AIP attacks from developing. Your plan may include:

- **Identifying and avoiding AIP triggers** – substances and situations that may trigger an attack, and **keeping a log** of your attacks and what may have triggered them.
- **Exercising moderately and eating a healthy, well-balanced diet,** avoiding low-carbohydrate diets.
- **Talking to your family and friends** about your AIP. The more they know about AIP, the more they can understand what you are going through and support you.
- **Developing a list of friends and neighbors** to call when you need extra help. And when you need help, being specific about what you need, such as taking you to the doctor, caring for your pet, or bringing in your mail.
- Finding **additional information and support** through the American Porphyria Foundation.
- **Encouraging family members** to talk to their doctors about **getting tested for AIP** and finding out if they are at risk for having AIP attacks.

Develop an emergency plan

The goal of your emergency plan will be to get prompt treatment when you have an AIP attack. Having a plan in place will help ensure that you get the care you need when you need it.

Here are some questions to ask your doctor when developing your emergency plan:

- Whom should I call if I have an AIP attack? Do I have a phone number to contact my doctor?
- What should I do if my doctor is not available?
- Where should I go – hospital, infusion center, or doctor's office – if I have an attack?
- Do I have a friend or family member who will take me to the facility?
- How should I prepare myself for an attack when I'm out of town? Are there hospitals in the area with doctors who treat AIP?
- What should I do if I have warning symptoms that may lead to an attack?

Also ask your doctor to write a **"Dear doctor" letter** that explains your diagnosis and provides instructions on what to do if you have an AIP attack. Include contact information for your doctor or other support resources in the letter. You should carry the letter with you at all times so that you can give it to healthcare providers who may not be familiar with AIP attacks or their treatment.

Where can you find more information and support?

These organizations can provide more information about AIP:

American Porphyria Foundation
www.porphyriafoundation.org
1-866-APF-3635 (273-3635)
info@porphyriafoundation.org

The mission of the American Porphyria Foundation (APF) is to improve the health and well-being of individuals and families affected by all types of porphyria, including AIP. The APF focuses on education, advocacy, support services, and research for the prevention, treatment, and cure of the porphyrias.

The Porphyrias Consortium
www.rarediseasesnetwork.org/cms/porphyrias

The mission of The Porphyrias Consortium, part of the Rare Diseases Clinical Research Network, is to expand knowledge about the porphyrias and thereby benefit patients and their families. The Porphyrias Consortium partners with the APF to develop new strategies and methods for diagnosing, treating, and preventing illness and disability resulting from the porphyrias, including AIP. Six of the leading porphyria centers in the United States, as well as seven satellite sites, are part of the consortium.

Recordati Rare Diseases Inc. • Lebanon, NJ 08833
www.recordatirarediseases.com/us PP-PHT-US-0210

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PANHEMATIN safely and effectively. See full prescribing information for PANHEMATIN.

PANHEMATIN®
(hemin for injection)

For intravenous infusion only.

Initial U.S. Approval: 1983

INDICATIONS AND USAGE

PANHEMATIN is a hemin for injection indicated for 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. (1)

Limitations of Use

- Before administering PANHEMATIN, consider an appropriate period of carbohydrate loading (i.e., 400 g glucose/day for 1 to 2 days). (1)
- PANHEMATIN is not effective in repairing neuronal damage due to progression of porphyria attacks. (1)

DOSAGE AND ADMINISTRATION

For intravenous infusion only.

- Dose (2.1)
  - 1 to 4 mg/kg/day for 3 to 14 days based on the clinical signs. The standard dose in clinical practice is 3 to 4 mg/kg/day.
  - Repeat dose in more severe cases no earlier than every 12 hours. Do not exceed 6 mg/kg in any 24 hour period.
- Administration (2.2)
  - Use sterile 0.45 micron or smaller filter to remove any undissolved particulate matter.
  - The dose may be administered directly from the vial over a period of at least 30 minutes.
  - After the infusion, flush the vein with 100 mL of 0.9% NaCl.

DOSAGE FORMS AND STRENGTHS

PANHEMATIN is available as a sterile, lyophilized powder for reconstitution for injection. Each vial contains the equivalent of 350 mg hemin, 240 mg sodium carbonate and 335 mg of sorbitol.

When mixed as directed with Sterile Water for Injection, USP, each 48 mL provides the equivalent of approximately 336 mg hematin (7 mg/mL). (3)

CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to PANHEMATIN. (4)

WARNINGS AND PRECAUTIONS

- Phlebitis is possible. Utilize a large arm vein or a central venous catheter for administration to minimize the risk of phlebitis. (5.1)
- Elevated iron and serum ferritin may occur. Monitor iron and serum ferritin in patients receiving multiple administrations of PANHEMATIN. (5.2)
- PANHEMATIN has transient and mild anticoagulant effect. Avoid concurrent anticoagulant therapy. (5.3)
- Reversible renal shutdown has been observed with an excessive hematin dose (12.2 mg/kg in a single infusion). Strictly follow recommended dosage guidelines. (5.4)
- PANHEMATIN may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.5)

ADVERSE REACTIONS

Most common adverse reactions in >1% of patients are headache, pyrexia, infusion site reactions, and phlebitis. (6.1)

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

DRUG INTERACTIONS

Avoid CYP inducing drugs such as estrogens, barbituric acid derivatives and steroid metabolites which induce δ-aminolevulinic acid synthetase 1 (ALAS1) through a feedback mechanism. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PANHEMATIN is a hemin for injection 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) [*See Dosage and Administration (2.1)*].
- 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.

2 DOSAGE AND ADMINISTRATION

For intravenous infusion only.

2.1 Dosing

- 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.
- The dose of PANHEMATIN is 1 to 4 mg/kg/day of hematin for 3 to 14 days based on the clinical signs. The standard dose in clinical practice is 3 to 4 mg/kg/day. In more severe cases this dose may be repeated no earlier than every 12 hours. Do not exceed 6 mg/kg of hematin in any 24 hour period. After reconstitution each mL of PANHEMATIN contains the equivalent of approximately 7 mg of hematin (see dosage calculation table below).

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

- 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

2.2 Preparation and Administration

- Because PANHEMATIN contains no preservative and undergoes rapid chemical decomposition in solution, it must be reconstituted immediately before use.
- 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.
- 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.
- Do not add other drug or chemical agent to a PANHEMATIN fluid admixture.
- 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.

3 DOSAGE FORMS AND STRENGTHS

PANHEMATIN is available as a sterile, lyophilized black powder in single dose dispensing vials. Each vial contains the equivalent of 350 mg hemin, 240 mg sodium carbonate and 335 mg of sorbitol. When mixed as directed with Sterile Water for Injection, USP, each 48 mL provides the equivalent of approximately 336 mg hematin (7 mg/mL).

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Phlebitis

A large arm vein or a central venous catheter should be utilized for the administration of PANHEMATIN to minimize the risk 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. [*See Dosage and Administration (2.2)*]

5.2 Iron and Serum Ferritin

Because increased levels of iron and serum ferritin have been reported in post-marketing experience, physicians must monitor iron and serum ferritin in patients receiving multiple administrations of PANHEMATIN [*See Adverse Reactions (6.2)*]. In case of elevated iron or serum ferritin levels, consider iron chelation therapy.

5.3 Anticoagulant Effects

Because PANHEMATIN has exhibited transient, mild anticoagulant effects during clinical studies, avoid concurrent anticoagulant therapy. The extent and duration of the hypocoagulable state induced by PANHEMATIN has not been established.

5.4 Renal Effects

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. No worsening of renal function has been seen with administration of recommended dosages of hematin.

5.5 Transmissible Infectious Agents

Because PANHEMATIN is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creuzfeldt-Jacob disease (vCJD) agent, and theoretically the Creuzfeldt-Jacob disease (CJD) agent. The risk that this product may 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, this product can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in the product.

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 at 1-888-575-8344.

6 ADVERSE REACTIONS

The most common adverse reactions (occurring in >1% of patients) are: headache, pyrexia, infusion site reactions, and phlebitis.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety 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. Of those, 111 patients were administered hemin for treatment of 305 acute porphyria attacks and to 40 patients for prophylaxis. The majority (92%) of patients were Caucasian. Most (72%) were female; all adult patients had a mean age ± SD of 40.3 ± 12.3 years. Proportionally more females (15 out of 19) received prophylaxis or a combination of acute treatment and prophylaxis (19 out of 21). For the treatment of acute attacks, patients received 2 to 4 mg/kg/day PANHEMATIN intravenously for 1 to 9 doses. For prophylaxis patients, the most common doses were weekly or biweekly infusions. Table 1 summarizes adverse reactions occurring in >1% of patients treated with PANHEMATIN, categorized by body system and order of decreasing frequency.

Table 1: Adverse Reactions in >1% of Patients Treated with PANHEMATIN

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%)

6.2 Postmarketing Experience

The following adverse reactions associated with the use of PANHEMATIN were identified in open-label clinical trials or postmarketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: thrombocytopenia, coagulopathy (including prolonged prothrombin time and prolonged partial thromboplastin time), and hemolysis

Immune System Disorders: hypersensitivity reactions including a report of infusion-related anaphylactoid reaction presenting as circulatory collapse

Vascular Disorders: injection site venous thrombosis including some that occurred in large veins such as venae cavae

General Disorders and Administration Site Conditions: infusion site reactions (such as erythema, pain, bleeding and extravasation)

Metabolism and Nutrition Disorders: iron overload and serum ferritin increased [*See Warnings and Precautions (5.2)*]

7 DRUG INTERACTIONS

PANHEMATIN therapy is intended to limit the rate of porphyria/heme biosynthesis possibly by inhibiting the enzyme δ-aminolevulinic acid synthetase 1 (ALAS1) [*See Clinical Pharmacology (12.1)*]. Most of the heme synthesized in liver is used for the production of cytochrome P450 (CYP) enzymes. Therefore, avoid CYP inducing drugs (such as estrogens, barbituric acid derivatives and steroid metabolites) while on PANHEMATIN therapy, because these drugs increase the activity of ALAS leading to induction of ALAS1 through a feedback mechanism.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

About 50% of the women with acute intermittent porphyria experience an acute attack of porphyria in pregnancy and/or the puerperium. It is most severe in early pregnancy and the puerperium, and can result in fatal outcome. Although anecdotal evidence suggests safe use of hematin during pregnancy, the available human data is not sufficient to establish the presence or absence of drug-associated risk. 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. PANHEMATIN should be given to a pregnant woman only if clearly needed.

Avoid administering hematin in severe pre-eclampsia because of a theoretical risk of potentiation of the coagulation disorder [*see Warnings and Precautions (5.3)*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

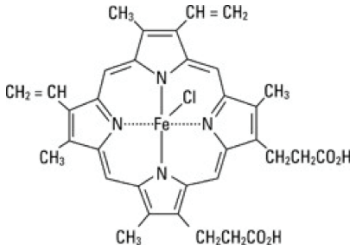
Clinical data for subjects aged 65 and over was not sufficient to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient 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.

10 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 [*see Warnings and Precautions (5.4)*]. Treatment of this case consisted of ethacrynic acid and mannitol.

11 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 and hematin are iron containing metalloporphyrin complexes with either bound chloride or hydroxide ions, respectively. 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 formatted as a sterile, lyophilized powder for intravenous administration after reconstitution. Each dispensing vial of PANHEMATIN contains the equivalent of 350 mg hemin, 240 mg sodium carbonate and 335 mg of sorbitol. The pH may have been adjusted with hydrochloric acid. When mixed as directed with Sterile Water for Injection, USP, each 48 mL provides the equivalent of approximately 336 mg hematin (7 mg/mL). The product contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

PANHEMATIN 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.

12.3 Pharmacokinetics

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.

Other aspects of human pharmacokinetics have not been defined.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

The effectiveness of PANHEMATIN for the amelioration of recurrent attacks of acute intermittent porphyria was evaluated in five open-label studies, one compassionate-use study, case reports, and an observational study investigating patient reported outcomes in patients with acute porphyrias.

Open-Label Studies

In these initial 5 open-label studies,[1-5] 99 patients with acute porphyrias (72 with AIP) were treated with 3-4 mg/kg/day of hemin once or twice daily. Of the 99 patients in these studies, 30 received prior or concomitant glucose administration. Patients experienced a clinical response in 85.5% (141/165) of treatment courses (Figure 1). Clinical response was defined by improvement of symptoms and reduction in pain. All patients experienced a chemical response which was defined as normalization of urinary aminolevulinic acid (ALA) and porphobilinogen (PBG).

Watson et al.[1] studied the use of hemin treatment in 15 patients with acute porphyrias, of whom 11 were with AIP. Seven patients were female and four were male with an age range of 19-45 years with biochemical evidence of AIP. Preparations of 4 mg/kg IV of hemin were infused at 12- or 24-hour intervals for 1 to 4 days after trials of glucose of various durations and dosages in all patients. All patients, with exception of one, experienced a clear clinical response most of which was rapid after hemin infusion. All patients also demonstrated a chemical response based on 58%-100% reduction in urinary ALA and PBG levels.

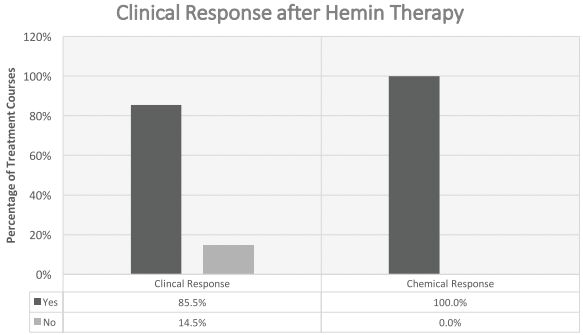
Pierach et al.[2] examined the use of 2 to 4 mg/kg of hemin IV in 57 patients with acute porphyrias, of whom 43 were with AIP. Out of 82 individual acute intermittent porphyria attacks with 476 hemin infusions (82 treatment courses) administered, a clinical response was seen in 74 (90%) acute attacks. A chemical response was seen for those patients who had elevated urinary ALA and PBG levels prior to hemin treatment.

McColl et al.[3] reported the use of 4 mg/kg of hemin IV given either every 12 or 24 hours for three to five days in the treatment of 13 attacks of acute porphyria in eight patients. Seven of these 8 patients had AIP. Five patients with AIP were female and two were male with a mean age of 25 years (range 19-31 years). All patients had biochemical and clinical evidence of an attack of acute porphyria at the time of hemin administration. All patients had a chemical response of approximately 50% reduction in urinary ALA and PBG from pre-treatment values. In addition, clinical response was seen after hemin treatment in a total of 7 attacks in 5 AIP patients.

Lamon et al.[4] reported on 12 patients with acute porphyrias, of whom 11 were with AIP. These AIP patients received 190 infusions of approximately 2 to 4 mg/kg of hemin IV given every 12 or 24 hours for 3 to 13 days as 20 separate courses of treatment, when high carbohydrate intake (300 g for a minimum of 72 hours) and supportive measures were unsuccessful. Urinary ALA and PBG levels were collected as well as clinical signs and symptoms of AIP recorded. Out of 20 treatment courses for acute attacks, there was a clinical response in 14. All patients had significant reductions in ALA and/or PBG levels after hemin treatment (p-value in the range from less than 0.001 to 0.05).

In another study by Lamon et al.[5] seven patients with acute attacks of porphyria were administered 11 hemin courses (each course: 1 mg/kg every 24 hours for 3 to 13 days). Before and during hemin administration, patients were maintained on a 250-300 g/24H carbohydrate diet. Patients had elevated urinary ALA and PBG treatment and clinical evidence of an acute attack. Chemical response of a decrease in ALA and PBG occurred in every patient (except one PBG value in one patient) when treatment lasted 5 days or longer ($p<0.001$).

Figure 1: Efficacy Data on Hemin in Acute Intermittent Porphyria from 5 Open-Label Studies



Compassionate Use Study

In the compassionate use, multi-center, open-label, non-comparative study[6], 130 patients were enrolled with a diagnosis of acute porphyria and were treated with hemin. The patients were administered hemin for acute attacks [N=90 (69%)], prophylaxis [N=19 (15%)], or both [N=21 (16%)]. There was a subset of patients in the "both" group (acute attacks and prophylaxis) who were treated for acute attacks prior to receiving prophylactic treatment. Seventy-two percent of the patients were female and 28% were male. Hemin was administered to 111 patients (enrolled in the "acute attack" and the "both" treatment groups) for the treatment of 305 acute attacks and to 40 patients (enrolled in the "prophylaxis" and the "both" treatment groups) for prophylactic treatment. Out of the 40 patients who received prophylaxis, 19 received prophylaxis only and 21 patients were treated for up to 3 acute attacks prior to receiving prophylactic treatment. Prophylaxis treatment varied greatly in frequency with the most common hemin regimen given once a week. 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.

A physician-assessed clinical response was achieved for all acute attacks in 81 (73%) of 111 patients. Ninety-four patients (85%) of 111 had ≥1 clinical response and 17 patients (15%) of 111 had no response. Among 31 of 40 patients who received hemin prophylaxis for >1 month, 21 (68%) did not require subsequent hemin treatment for acute attacks.

Case Reports

In 234 courses, patients received hemin therapy as normally prescribed by their physicians with the majority dosed between the recommended range of 3 mg/kg/day to 4 mg/kg/day for at least one course of treatment. In these patients, hemin treatment was administered immediately in 33% of recipients, within 1 day of symptom onset in 50%, and within 3 days in 75%. These groups were not mutually exclusive. Most patients [108/111 (97.3%)] received a dose of at least 3 mg/kg/day and only 3 patients (2.7%) received a dose of hemin less than 2 mg/kg/day. There were 6 patients (5.4%) who were administered doses exceeding 6 mg/kg/day for 1 or more treatment courses.

Observational Patient Reported Outcomes Study

An observational study investigated patient reported outcomes in 108 patients with acute porphyrias.[7] Out of 108 patients, 90 patients were with AIP and reported the following:

- 55% percent reported having received hemin during acute attacks, and 74% of these patients assessed PANHEMATIN therapy as very successful in the treatment of abdominal pain and other symptoms.
- 50% reported having received treatment with opiates during an acute attack, and 44% of these patients reported that opiates were effective.

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 ($p=0.0049$).

15 REFERENCES

1. Watson, CJ, et al., Use of Hematin in the Acute Attack of the "Inducible" Hepatic Porphyrias, Adv Intern Med. 1978;23:265-286.
2. Pierach CA, Bossenmaier I, Cardinal R, Weimer M, Watson CJ. Hematin therapy in porphyric attacks. Klinische Wochenschrift. 1980;58(16):829-832.
3. McColl KE, Moore MR, Thompson GG, Goldberg A. Treatment with haematin in acute hepatic porphyria. The Quarterly journal of medicine. 1981;50(198):161-174.
4. Lamon, JM, Hematin Therapy for Acute Porphyria, Medicine. 1979;58(3):252-269.
5. Lamon JM. Hematin Therapy in Acute Porphyria. Clin Res. 1977;25(3):471A.
6. Anderson, KE and Collins, S, Open-Label Study of Hemin for Acute Porphyria: Clinical Practice Implications. American Journal of Medicine. 2006;119(9):801.
7. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell M, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014;127(12):1233-1241.

16 HOW SUPPLIED/STORAGE AND HANDLING

PANHEMATIN is supplied as a sterile, lyophilized black powder in single dose dispensing vials (NDC 55292-702-54) in a carton (NDC 55292-702-55).

The vial stopper contains natural rubber latex.

Store lyophilized powder at 20-25°C (68-77°F).

17 PATIENT COUNSELING INFORMATION

- Advise the patient not to take drugs such as estrogens (e.g., oral contraceptives), barbiturates (drugs which help them to sleep and drugs sometimes used to treat epilepsy) or steroids (body hormone-like drugs), because this can trigger an attack or make the attack worse.

- Advise a female patient to inform the prescriber if she is pregnant or planning to become pregnant.

Manufactured by:
Sagent Pharmaceuticals, Inc.
Raleigh, NC 27616

For:
Recordati Rare Diseases Inc.
Lebanon, NJ 08833, U.S.A.

U.S. Lic. No. 1899

RECORDATI RARE DISEASES GROUP

750-11003-1

PP-PHT-US-0213