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Barhemsys® (amisulpride) injection 2.5mg/mL

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Indications

Barhemsys is a selective dopamine-2 (D_2) and dopamine-3 (D_3) receptor antagonist indicated in adults for:

- prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class
- treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis

Select Important Safety Information

Contraindication

Barhemsys is contraindicated in patients with known hypersensitivity to amisulpride.

Please see Important Safety Information on the last page and full Prescribing Information.

Barhemsys® (amisulpride) injection 2.5mg/mL

General

- Why is the indication limited to adults?

  The study populations in the prospective trials were composed of adults.[1-4] Safety and effectiveness of Barhemsys® in pediatric patients has not been established.[5]

- Since there are multiple pathways involved in PONV, why target dopamine?

  Activation of several receptors leads to nausea or vomiting. Most antiemetic drugs exert their effects by blocking one or more of these receptors.[6]

  Dopamine-2 (D_2) receptors in the stomach appear to mediate the inhibition of gastric motility that occurs during nausea and vomiting, and they participate in reflexes that relax the upper portion of the stomach and delay gastric emptying. D_2 receptors are also implicated in emetic signaling at the chemoreceptor trigger zone (CTZ) and in the nucleus tractus solitarii (NTS).[6] Additionally, animal data suggest activation of dopamine-3 (D_3) receptors potentiate the vomiting action of D_2 receptors.[7]

  Guidelines suggest that, if prophylaxis fails, an antiemetic from a different class than the prophylactic drug should be used for rescue treatment. Because serotonin ($5\text{-}HT_3$) antagonists have been widely used for PONV prophylaxis, dopamine antagonism is an attractive mechanism for a rescue antiemetic.[8]

Clinical Trials

- How was the efficacy of Barhemsys studied?

  The efficacy of Barhemsys for the prevention of PONV was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials in patients undergoing general anesthesia and elective surgery. In both trials, patients were administered Barhemsys at the induction of anesthesia.[2,3,5] In Study 1 (N=342), patients received monotherapy with Barhemsys.[3,5] In Study 2 (N=1147), patients received Barhemsys in combination with 1 other intravenously administered nondopaminergic antiemetic.[2,5]

  The primary efficacy endpoint in both prevention trials was Complete Response, defined as absence of any episode of emesis or use of rescue medication within the first 24 hours postoperatively.[2,3,5]

  The efficacy of Barhemsys 10 mg as a single dose was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials in patients experiencing PONV after general anesthesia and elective surgery.[1,4,5] Study 3 (N=369) enrolled patients who had not received PONV prophylaxis.[4,5] Study 4 (N=465) enrolled patients with moderate to high risk of PONV after they failed antiemetic prophylaxis with an antiemetic of another class.[1,5]

  For the treatment and rescue treatment trials, the primary efficacy endpoint was Complete Response defined as absence of any episode of emesis or use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes).[1,4,5]

- As a PONV rescue treatment, why was Barhemsys evaluated against placebo instead of an active comparator drug?

  Two doses of Barhemsys were studied against placebo in rescue treatment, clearly establishing the 10 mg dose as effective and safe.[1] The regulatory requirement is to conduct placebo-controlled trials unless the use of placebo is deemed unethical based on disease type. It is important to study any new entity against placebo when there is no existing gold standard or approved treatment. In such settings, placebo is the appropriate comparator, allowing for the examination of efficacy, safety, and optimal dosing. Prior to Barhemsys, no other antiemetic agent was approved for rescue treatment and no other agent has positive data (superior to placebo).

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Safety

- Why does Barhemsys have a warning for QT prolongation?

  The safety of patients is a primary concern and consideration when choosing any product. Barhemsys is a dopamine antagonist and can cause dose- and concentration-dependent QT prolongation.[5]

  A thorough QT study was completed to measure the clinical impact of Barhemsys 5 mg and 40 mg on QT prolongation.[5,9] After dosing with Barhemsys 5 mg, no subject experienced a QTcF greater than 450 milliseconds or a change from baseline greater than 30 milliseconds. The largest QTcF recorded with amisulpride 40 mg was 472 milliseconds, and the largest increase from baseline was 36 milliseconds.[9,10]

  Avoid Barhemsys in patients with congenital long QT syndrome and in patients taking droperidol.[5]

  Electrocardiogram (ECG) monitoring is recommended in patients with preexisting arrhythmias/cardiac conduction disorders, electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), congestive heart failure, and in patients taking other medicinal products (eg, ondansetron) or with other medical conditions known to prolong the QT interval. No boxed warning was issued for Barhemsys.[5]

- What were the most common side effects of Barhemsys reported in the pivotal trials?

  Common adverse reactions reported in ≥ 2% of adult patients who received Barhemsys 5 mg (N=748) and at a higher rate than placebo (N=741) in clinical trials for the prevention of PONV were: chills (4% vs 3%), hypokalemia (4% vs 2%), procedural hypotension (3% vs 2%), and abdominal distention (2% vs 1%).[5]

  The most common adverse reaction, reported in ≥ 2% of adult patients who received Barhemsys 10 mg (N=418) and at a higher rate than placebo (N=416), in clinical trials for the treatment of PONV was infusion site pain (6% vs 4%).[5]

- Does Barhemsys cause sedation?

  Barhemsys is nonsedating. Based on data from the PONV clinical program, treatment-related sedation or sedation-like reactions were not reported in 922 patients who received 5-40 mg of amisulpride.[5,10]

- Can Barhemsys be co-administered with a 5-HT_3 receptor antagonist, such as ondansetron?

  There are no restrictions regarding co-administration of Barhemsys and a 5-HT_3 antagonist. ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (e.g., ondansetron).[5]

- Since female sex is a major risk factor for PONV, what data are there on the use of Barhemsys concomitant with pregnancy and/or lactation?

  Available data with amisulpride use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant and lactating women were excluded from the Barhemsys clinical trials for management of PONV.[1-4] In animal reproduction studies, there were no adverse developmental effects observed with oral administration of amisulpride in rats and rabbits during the period of organogenesis at exposures about 43 and 645 times, respectively, the exposure delivered by the highest recommended human dose.[5]

  Amisulpride is present in human milk. There are no reports of adverse effects on the breastfed child and no information on the effects on milk production. Barhemsys may result in an increase in serum prolactin levels, which may lead to a reversible increase in maternal milk production. In a clinical trial, serum prolactin concentrations in females (n=112) increased from a mean of 10 ng/mL at baseline to 32 ng/mL after Barhemsys treatment and from 10 ng/mL to 19 ng/mL in males (n=61). No clinical consequences due to elevated prolactin levels were reported.[5]

  To minimize exposure to a breastfed infant, lactating women may consider interrupting breastfeeding and pumping and discarding breast milk 48 hours after receiving a dose of Barhemsys.[5]

- How do I report an adverse event?

  To report a suspected adverse reaction, contact Acacia Pharma at 1-877-357-9237 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Administration

- How is Barhemsys administered?

  Barhemsys is a ready-to-use PONV therapy requiring no special preparation (no reconstitution, dilution, or refrigeration).[5]

  The approved dose of Barhemsys for[5]:

  - Rescue treatment of PONV, despite prophylaxis, is 10 mg as a single IV dose administered over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure; this requires the use of one 10 mg vial (1 vial x 10 mg/4 mL) or two 5 mg vials (2 vials x 5 mg/2 mL)
  - Prevention of PONV is 5 mg as a single IV dose administered over 1-2 minutes at the time of induction of anesthesia (1 vial x 5 mg/2 mL)

- Can Barhemsys 5 mg be used for rescue treatment of PONV after failed prophylaxis?

  Barhemsys is the first and only FDA-approved antiemetic for the rescue treatment of PONV in patients who have failed prophylaxis, with demonstrated safety and efficacy at the recommended 10 mg dose.[5] In the prospective, randomized trial, Barhemsys 5 mg was tested because this dose previously demonstrated effectiveness as a prophylaxis for PONV.[1-3] Barhemsys 10 mg was also investigated in case a higher dose might be needed for treatment.[1]

  In the prospective study, Barhemsys 10 mg was superior to placebo at treating PONV after failed prophylaxis, whereas 5 mg was not superior to placebo.[1] Therefore, Barhemsys 5 mg is not an FDA-approved dose for rescue treatment.[5]

- Can Barhemsys be administered with other antiemetics?

  Barhemsys can be administered with other antiemetics. In the prospective combination prophylaxis trial, Barhemsys was co-administered with ondansetron, dexamethasone, betamethasone, and promethazine.[2] ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (eg, ondansetron).[5]

Storage and Handling

- How is Barhemsys supplied?

  Barhemsys is supplied as a 5 mg vial and a 10 mg vial as follows:

  - NDC 71390-125-20: a package of 10 cartons. Each carton (NDC 71390-125-21) contains one single-dose vial of clear, colorless, sterile solution of Barhemsys injection, 5 mg in 2 mL (2.5 mg/mL)[5]
  - NDC 71390-125-50: a package of 10 cartons. Each carton (NDC 71390-125-51) contains one single-dose vial of clear, colorless, sterile solution of Barhemsys injection, 10 mg in 4 mL (2.5 mg/mL)[5]

- What are the storage and handling conditions of Barhemsys?

  Store vials at 20°C to 25°C (68°F to 77°F). Protect from light. Administer Barhemsys within 12 hours after the vial is removed from the protective carton.[5]

- Why is Barhemsys in clear vials if it is light sensitive?

  Barhemsys was studied in clear vials before knowing the product was sensitive to light. Barhemsys should be protected from light and must be administered within 12 hours after removal from the protective carton.[5]

Indications

Barhemsys is a selective dopamine-2 (D_2) and dopamine-3 (D_3) receptor antagonist indicated in adults for:

- prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class
- treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis

Important Safety Information

Contraindication

Barhemsys is contraindicated in patients with known hypersensitivity to amisulpride.

QT Prolongation

Barhemsys causes dose- and concentration-dependent prolongation of the QT interval. The recommended dosage is 5 mg or 10 mg as a single intravenous (IV) dose infused over 1 to 2 minutes.

Avoid Barhemsys in patients with congenital long QT syndrome and in patients taking droperidol.

Electrocardiogram (ECG) monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders, electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval.

Adverse Reactions

Common adverse reactions reported in ≥ 2% of adult patients who received Barhemsys 5 mg (N=748) and at a higher rate than placebo (N=741) in clinical trials for the prevention of PONV were: chills (4% vs. 3%), hypokalemia (4% vs. 2%), procedural hypotension (3% vs. 2%), and abdominal distention (2% vs. 1%).

Serum prolactin concentrations were measured in one prophylaxis study where 5% (9/176) of Barhemsys-treated patients had increased blood prolactin reported as an adverse reaction compared with 1% (1/166) of placebo-treated patients.

The most common adverse reaction, reported in ≥ 2% of adult patients who received Barhemsys 10 mg (N=418) and at a higher rate than placebo (N=416), in clinical trials for the treatment of PONV was infusion site pain (6% vs. 4%).

Use in Specific Populations

Pregnancy

Available data with amisulpride use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Lactation

Amisulpride is present in human milk. There are no reports of adverse effects on the breastfed child and no information on the effects of amisulpride on milk production.

Barhemsys may result in an increase in serum prolactin levels, which may lead to a reversible increase in maternal milk production. In a clinical trial, serum prolactin concentrations in females (n=112) increased from a mean of 10 ng/mL at baseline to 32 ng/mL after Barhemsys treatment and from 10 ng/mL to 19 ng/mL in males (n=61). No clinical consequences due to elevated prolactin levels were reported.

To minimize exposure to a breastfed infant, lactating women may consider interrupting breastfeeding and pumping and discarding breast milk for 48 hours after receiving a dose of Barhemsys.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

- Barhemsys causes dose- and concentration-dependent QT prolongation. To avoid potential additive effects, avoid use of Barhemsys in patients taking droperidol.
- ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (e.g., ondansetron).
- Reciprocal antagonism of effects occurs between dopamine agonists (e.g., levodopa) and Barhemsys. Avoid using levodopa with Barhemsys.

Please see full Prescribing Information.

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1. Habib AS, et al. *Anesthesiology.* 2019;130(2):203-212. **2.** Kranke P, et al. *Anesthesiology.* 2018;128(6):1099-1106. **3.** Gan TJ, et al. *Anesthesiology.* 2017;126(2):268-275. **4.** Candiotti KA, et al. *Anesth Analg.* 2019;128(6):1098-1105. **5.** Barhemsys [Prescribing Information], Indianapolis, IN. Acacia Pharma; 2021. **6.** Golembiewski J, et al. *Am J Health-Sys Pharm.* 2005;62:1247-1260. **7.** Darmani NA, et al. *J Neural Transm.* 1999;106(11-12):1045-1061. **8.** Gan TJ, et al. *Anesth Analg.* 2020;131(2):411-448. **9.** Taubel J, et al. *Br J Clin Pharmacol.* 2017;83:339-348. **10.** Acacia Pharma. Data on File.