EAGLE PHARMACEUTICALS

Barhemsys® (amisulpride) injection 2.5mg/mL

Treat Breakthrough PONV Promptly and Aggressively With Barhemsys®

For additional information regarding Barhemsys, please visit **Barhemsys.com**

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 last page and full Prescribing Information.

Unmet Need in PONV

PONV is a common complication of surgery and anesthesia despite prophylaxis

- In high-risk patients, the PONV rate can be **as high as 80%**[1,2]
  - Despite antiemetic prophylaxis, >30% of high-risk patients may still experience PONV[3,4]
- In patients who have PONV, including those in the rescue setting, **more patients may experience nausea** (>95%) than vomiting (~20%)[4,5]
- Nausea and vomiting in the PACU may result in **delayed PACU discharge**, **unanticipated hospitalization**, and **prolonged hospital stay**[1,5-7]
- Additionally, PONV is a major cause of **patient dissatisfaction** following anesthesia, even considered worse than pain[8-10]

Treatment for established PONV should be prompt and aggressive

- The 2020 consensus guidelines **recommend to treat breakthrough PONV promptly and aggressively with an antiemetic from a different class** than that used for prophylaxis[1]
  - **Repeating a medication** from the same pharmacological class within 6 hours of administration **does not improve efficacy**[1]

PACU=postanesthesia care unit. PONV=postoperative nausea and vomiting.

Clinical Trials Overview

Barhemsys was evaluated in 4 pivotal clinical trials (N=2,323)[11]

PROPHYLAXIS FOR PONV

MONOTHERAPY

Study 1 (N=342) patients received Barhemsys monotherapy[11,12]

COMBINATION THERAPY

Study 2 (N=1147) patients received Barhemsys in combination with 1 other intravenously administered, nondopaminergic antiemetic[11,13]

TREATMENT FOR PONV

TREATMENT

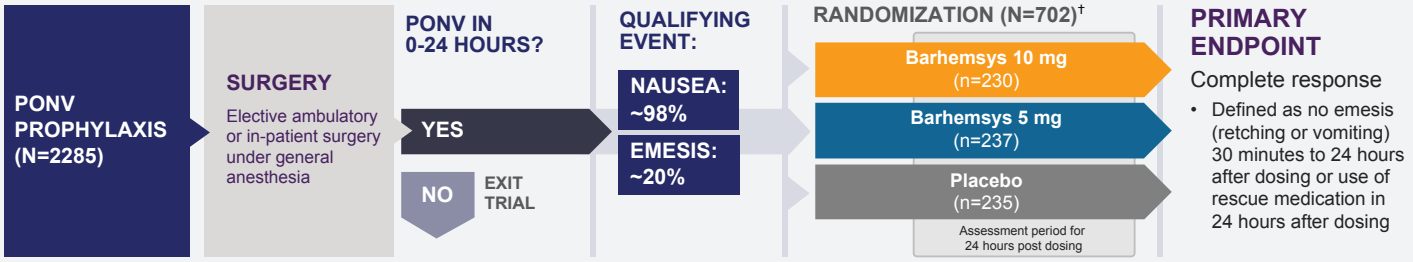
Study 3 (N=369) was conducted in patients who had not received PONV prophylaxis[11,14]

RESCUE TREATMENT

Study 4 (N=465) was conducted in patients with moderate to high risk of PONV who failed antiemetic prophylaxis with an antiemetic of another class[4,11]

Rescue treatment trial design[4,11]

Study 4 was a randomized, double-blind, placebo-controlled, multicenter trial evaluating Barhemsys for the treatment of PONV in adult patients who had undergone elective ambulatory or inpatient surgery under general anesthesia and failed prior antiemetic prophylaxis.*



Barhemsys 5 mg is not an approved dose for treatment of PONV.

Risk factors: >90% of patients had 3-4 risk factors; these percentages were similar between treatment groups.‡

Prespecified secondary endpoints included incidence of emesis and rescue medication use, nausea burden, time to treatment failure, time spent in PACU after dosing, and overall length of hospital stay after dosing.

*Patients had received PONV prophylaxis with 1 or more nondopaminergic antiemetic: a 5-HT_3 antagonist in 77%, dexamethasone in 65%, and another antiemetic class in 10%. Total IV anesthesia with propofol was not permitted, though a single dose at induction was allowed.
†Of the 702 patients randomized, 465 patients were evaluated to determine the efficacy of 10 mg Barhemsys as a rescue treatment. 235 patients were in the placebo group and 230 patients were in the Barhemsys 10 mg group.
‡Risk factors include female, past history of PONV or motion sickness, nonsmoker, and expected use of postoperative opioid analgesia.

Select Important Safety Information

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.

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Rescue Treatment Trial: Efficacy Results

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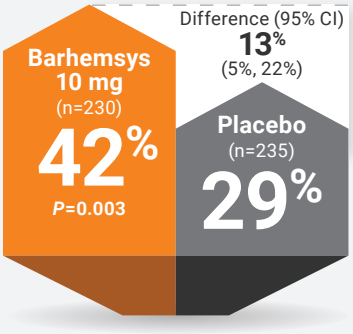
A single dose of Barhemsys 10 mg demonstrated efficacy in patients who failed PONV prophylaxis[4,11]

Primary endpoint: complete response



In patients who failed prophylaxis

42% (96/230) of Barhemsys 10 mg-treated patients met the criteria for complete response at 24 hours compared with **29% (67/235) of placebo**-treated patients

- **Difference** (95% confidence interval [CI]): **13%** (5%, 22%); *P*=0.003

The primary efficacy analysis was performed with the modified intention-to-treat (ITT) population (randomized patients who received study medication).

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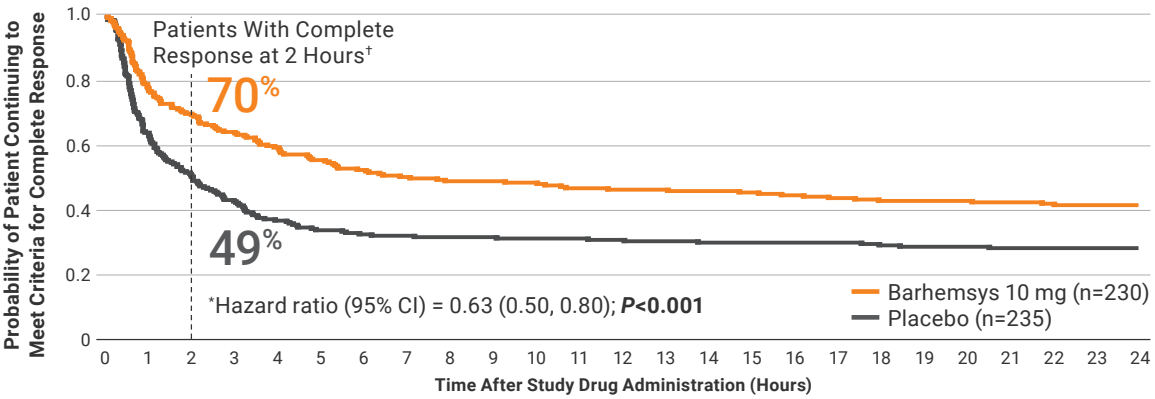
Kaplan-Meier curves of treatment success over time[4,*]



Patients With Complete Response at 24 Hours‡

42%

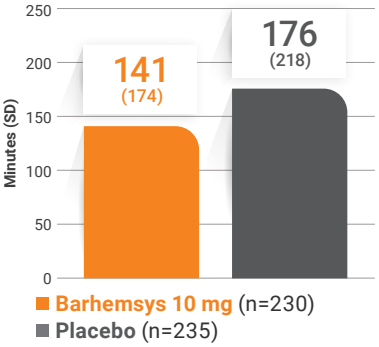
29%

‡*P*=0.003

†The secondary endpoint listed was prespecified. This endpoint was not adequately powered nor error controlled, and observed treatment differences cannot be regarded as statistically significant.

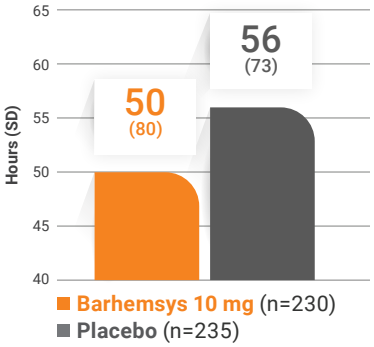
Secondary endpoints: PACU and hospital length of stay[4]

PACU length of stay, minutes



Barhemsys 10 mg-treated patients had **35 minutes shorter mean PACU length of stay** than placebo-treated patients

Hospital length of stay, hours



Barhemsys 10 mg-treated patients had **6 hours shorter mean hospital length of stay** than placebo-treated patients

The secondary endpoints listed were prespecified. These endpoints were not adequately powered nor error controlled, and observed treatment differences cannot be regarded as statistically significant.

Select Important Safety Information

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.

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

Barhemsys Safety Results

Common adverse reactions[11,*]

Treatment and rescue treatment of PONV clinical trials

	Barhemsys 10 mg (N=418)	Placebo (N=416)
Infusion site pain	6%	4%

Prevention of PONV clinical trials

	Barhemsys 5 mg (N=748)	Placebo (N=741)
Chills	4%	3%
Hypokalemia	4%	2%
Procedural hypotension	3%	2%
Abdominal distension	2%	1%

*Reported in ≥2% of patients treated with Barhemsys and at a higher rate than placebo.

Barhemsys is nonsedating[11,15]

Based on a post-hoc analysis of safety data from the clinical development program, 922 subjects could be evaluated for treatment-related sedation and none of them experienced sedation or sedation-like events.

Dosing and Administration[11]

PONV Rescue Treatment

1 Barhemsys 10 mg vial
(1 x 10 mg/4 mL)

10 mg as a single IV dose infused (IV push) over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure

PONV Prevention

1 Barhemsys 5 mg vial
(1 x 5 mg/2 mL)

5 mg as a single IV dose infused (IV push) over 1-2 minutes at the time of induction of anesthesia

Vials shown are not actual size.
IV=intravenous.

Barhemsys can be administered quickly[11]

- Barhemsys is a ready-to-use PONV therapy needing NO refrigeration, reconstitution, or dilution before administration
- Compatible to flush IV lines before and after Barhemsys administration with Water for Injection, 5% Dextrose Injection, 0.9% Sodium Chloride Injection, and Lactated Ringer's Solution†
- Protect from light; Barhemsys is subject to photodegradation; administer Barhemsys within 12 hours of removing the vial from the protective carton

†Also known as Ringer's Lactate Solution, Compound Sodium Lactate Solution, and Hartmann's Solution.

Select Important Safety Information

Use in Specific Populations (cont.)

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.

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

Barhemsys 10 mg for Rescue Treatment

Proven Efficacy

Treat breakthrough PONV **promptly and aggressively** with Barhemsys[1,4,11]

At 24 hours, **42% (96/230) of Barhemsys 10 mg-treated patients** met the criteria for complete response compared with 29% (67/235) of placebo-treated patients[4,11]

Barhemsys 10 mg-treated patients (n=230) had a **35-minute shorter mean PACU LOS** than placebo-treated patients (n=235)[4,*]

Nonsedating

Barhemsys is a **nonsedating selective dopamine-2 and dopamine-3 receptor antagonist,** offering a pharmacological option from a different class than agents commonly used in prophylaxis[1,4,11,15,†]

Established Safety Profile

The most common adverse reaction reported for Barhemsys 10 mg (N=418) and at a higher rate than placebo (N=416) was **infusion site pain** (6% vs 4%)[11]

*In the Phase 3 clinical trial of Barhemsys in patients who failed prophylaxis, Barhemsys 10 mg-treated patients (n=230) had a 35-minute shorter mean PACU length of stay and a 6-hour shorter mean hospital length of stay than placebo-treated patients (n=235). The secondary endpoints listed were prespecified. These endpoints were not adequately powered nor error controlled, and observed treatment differences cannot be regarded as statistically significant.

†Based on a post-hoc analysis of safety data from the clinical development program, 922 subjects could be evaluated for treatment-related sedation and none of them experienced sedation or sedation-like events.

LOS=length of stay.

Select Important Safety Information

Use in Specific Populations (cont.)

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.

1. Gan TJ, et al. *Anesth Analg*. 2020;131(2):411-448. **2.** Apfel CC, et al. *Anesthesiology*. 1999;91(3):693-700. **3.** White PF, et al. *Anesth Analg*. 2008;107:452-458. **4.** Habib AS, et al. *Anesthesiology*. 2019;130(2):203-212. **5.** Habib AS, et al. *Curr Med Res Opin*. 2006;22(6):1039-1099. **6.** Parra-Sanchez I, et al. *Can J Anaesth*. 2012;59(4):366-375. **7.** Gress K, et al. *Best Pract Res Clin Anaesthesiol*. 2020;34(4):681-686. **8.** Macario A, et al. *Anesth Analg*. 1999;89(3):652-658. **9.** Okuda C, et al. *Braz J Anesthesiol*. 2021;71(2):103-109. **10.** Eberhart LH, et al. *Br J Anaesth*. 2002;89(5):760-761. **11.** Barhemsys [package insert]. Indianapolis, IN: Acacia Pharma Inc; 2022. **12.** Gan TJ, et al. *Anesthesiology*. 2017;126:268-275. **13.** Kranke P, et al. *Anesthesiology*. 2018;128(6):1099-1106. **14.** Candiotti KA, et al. *Anesth Analg*. 2019;128(6):1098-1105. **15.** Acacia Pharma. Data on File.

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Important Safety Information

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QT Prolongation

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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.

To report SUSPECTED ADVERSE REACTIONS, contact Acacia Pharma at 1-877-357-9237 or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.

Please see full Prescribing Information.

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