Amisulpride for the Rescue Treatment of Postoperative Nausea or Vomiting in Patients Failing Prophylaxis

A Randomized, Placebo-Controlled, Phase III Trial

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Indications
BARHEMSYS is a selective dopamine-2 (D₂) and dopamine-3 (D₃) 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.
Background

- Although antiemetics are commonly used for postoperative nausea or vomiting (PONV) prophylaxis, the failure rate may exceed 30% in high-risk patients. BARHEMSYS® (amisulpride) is the first antiemetic to be approved for the rescue treatment of PONV after failed prophylaxis.
- Consensus guidelines specifically recommend that an antiemetic used to treat PONV should be from a different pharmacologic class than any drugs given prophylactically.
- Amisulpride is a selective dopamine-2 (D₂) and dopamine-3 (D₃) receptor antagonist, which offers a pharmacological option from a different class than agents commonly used in prophylaxis for PONV.
- This study by Habib et al was designed to assess the efficacy and safety of intravenous (IV) amisulpride in treating episodes of PONV after failed prophylaxis.

Study design

- A randomized, double-blind, parallel-group study across 23 international sites enrolled a total of 2285 adult patients undergoing open or laparoscopic surgery under general inhalational anesthesia and receiving antiemetic prophylaxis.
  - One or more non-dopamine antagonist antiemetics were allowed as prophylaxis.
  - Patients were excluded if they had received a dopamine-antagonist antiemetic.
- After receiving a prophylactic antiemetic, ~31% of patients (n=702) experienced PONV in the 24 hours after surgery and were randomized (1:1:1) to receive a single dose of 5 mg (n=237) or 10 mg (n=230) IV amisulpride or placebo (n=235).
- The primary efficacy endpoint was complete response defined as absence of any episode of emesis (vomiting or retching) or use of rescue medication within the first 24 hours after treatment, excluding emesis in the first 30 minutes.

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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Results

Primary endpoint: Complete response (95% confidence interval [CI])

- 42% (96/230) of amisulpride 10 mg-treated patients met the criteria for complete response at 24 hours compared to 29% (67/235) of placebo-treated patients ($P=0.003$).

Safety

- Rates of patients experiencing at least 1 treatment-emergent adverse event were 48.1% (113/235) for the placebo treatment group and 43.0% (99/230) for the amisulpride 10 mg treatment group.
- The most common adverse reaction, reported in ≥5% of adult patients who received amisulpride 10 mg (N=230) and at a higher rate than placebo (N=235), in clinical trials for the treatment of PONV was infusion site pain (5.2% vs 4.3%).

Conclusion

- This pivotal trial supported the approval of BARHEMSYS 10 mg for the rescue treatment of PONV for patients who failed prophylaxis.

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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 (3% vs. 2%).

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

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 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.

Renal Impairment
Avoid BARHEMSYS in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²). The pharmacokinetics of amisulpride in patients with severe renal impairment have not been adequately studied in clinical trials. Amisulpride is known to be substantially excreted by the kidneys, and patients with severe renal impairment may have increased systemic exposure and an increased risk of adverse reactions.

No dosage adjustment is necessary in patients with mild to moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m²).

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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