NEW DRUG APPROVAL

Brand Name	Barhesys®
Generic Name	amisulpride
Drug Manufacturer	Acacia Pharma Inc.

New Drug Approval

FDA Approval Date: February 26, 2020

Review Designation: None

Review Type: New Drug Application 209510

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

The term PONV is typically used to describe nausea and/or vomiting or retching in the post-anesthesia care unit (PACU) or in the immediate 24 postoperative hours.

Postoperative nausea and vomiting (PONV) is an enormous problem for patients recovering after surgery. About one-third of people experience vomiting, and half of them experience nausea. Nausea, retching, or vomiting usually occurs during the first 24-48 h after surgery in inpatients. In addition, vomiting or retching can result in wound dehiscence, esophageal rupture, aspiration, dehydration, increased intracranial pressure, and pneumothorax.

On average the incidence of nausea or vomiting after general anesthesia ranges between 25 and 30%. The highest risk patients for PONV appear to be young to middle-aged, non-smoking females with a history of PONV or motion sickness (all are independent risk factors). Extremes of age seem to be protective for postoperative nausea and vomiting. Meanwhile, there is an increased risk of PONV in female patients, in certain types of surgery.

According to this research, the total inpatients surgical cases in the 7 major markets was 52,032,174 in 2017. The total PONV cases in the 7 major markets was 16,980,822 in 2017.

Efficacy

Prevention of Postoperative Nausea and Vomiting:

The efficacy of BARHEMSYS for the prevention of PONV was evaluated in two randomized, double-blind, placebo-controlled, multi-center trials in patients undergoing general anesthesia and elective.

Study 1 (NCT01991860), patients received monotherapy with BARHEMSYS. It was conducted in the United States in 342 patients. The mean age was 54 years (range 21 to 88 years); 65% female; 87% White/Caucasian, 12% Black, and 1% Asian race.

Study 2 (NCT02337062), patients received BARHEMSYS in combination with one other intravenously administered, non-dopaminergic antiemetic (ondansetron, dexamethasone or betamethasone). It was conducted in the United States and Europe in 1,147 patients. The mean age was 49 years (range 18 to 91 years); 97% female; 75% White/Caucasian, 9% Black, 1% Asian, and 14% of unreported race.

The primary efficacy endpoint in both trials was Complete Response, defined as absence of any episode of emesis or use of rescue medication within the first 24 hours postoperatively. Results for both trials are shown in Table 3

	Study 1		Study 2	
	BARHEMSYS 5 mg (n=176)	**Placebo (n=166)**	**BARHEMSYS 5 mg with Another Antiemetic (n=572)**	**Placebo with Another Antiemetic (n=575)**
Complete response	78(44%)	54 (33%)	330 (58%)	268 (47%)
Difference (95% CI)	12 % (2%, 22%)		11 % (5%, 17%)	

Treatment of Postoperative Nausea and Vomiting:

The efficacy of BARHEMSYS 10 mg as a single dose was evaluated in two randomized, double-blind, placebo-controlled, multi-center trials in patients experiencing PONV after general anesthesia and elective surgery.

Study 3 (NCT02449291) enrolled patients who had not received prior PONV prophylaxis. It was conducted in 369 patients (mean age 47 years, range 19 to 82 years; 76% female; 82% White/Caucasian, 8% Black, 2% Asian, and 8% of unreported race).

Study 4 (NCT02646566) included patients who had received and failed PONV prophylaxis with an antiemetic of another class. It was conducted in 465 patients (mean age 46 years, range 18 to 85 years; 90% female; 82% White/Caucasian, 9% Black, 3% Asian, and 6% of unreported race)

For both 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)

	Study 3 (no prophylaxis)		Study 4 (prior prophylaxis)	
	BARHEMSYS 5 mg (n=188)	**Placebo (n=181)**	**BARHEMSYS 10 mg (n=230)**	**Placebo (n=235)**
Complete response	59 (31%)	39 (22%)	96 (42%)	67 (29%)
Difference (95% CI)	10% (1%, 19%)		13% (5%, 22%)	

Safety

ADVERSE EVENTS

Adverse reaction (1% to 10%)are :

- Cardiovascular: Procedural hypotension (3%)
- Endocrine & metabolic: Hypokalemia (4%), increased serum prolactin (5%)
- Gastrointestinal: Abdominal distention (2%)
- Local: Infusion-site pain (6%)
- Nervous system: Chills (4%)

WARNINGS & PRECAUTIONS

Concerns related to adverse effects:

Altered cardiac conduction: May cause dose- or concentration-dependent QTc prolongation; avoid in patients with congenital long QT syndrome.

Disease-related concerns:

Renal impairment: Use caution in patients with mild or moderate renal impairment; avoid use in patients with severe renal impairment.

Concurrent drug therapy issues:

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

CONTRAINDICATIONS

Hypersensitivity to amisulpride or any component of the formulation.

Clinical Pharmacology

MECHANISMS OF ACTION

Amisulpride is a selective dopamine-2 (D2) and dopamine-3 (D3) receptor antagonist. D2 receptors are located in the chemoreceptor trigger zone (CTZ) and respond to the dopamine released from the nerve endings. Activation of CTZ relays stimuli to the vomiting center which is involved in emesis. Studies in multiple species indicate that D3 receptors in the area postrema also play a role in emesis. Studies conducted in ferrets have shown that amisulpride inhibits emesis caused by apomorphine, with an estimated ED50 of less than 1 mcg/kg, subcutaneously; and inhibits cisplatin-induced emesis at 2 mg/kg and morphine-induced emesis at 3 to 6 mg/kg, when given intravenously. Amisulpride has no appreciable affinity for any other receptor types apart from low affinities for 5-HT2B and 5-HT7 receptors.

Dose & Administration

ADULTS

Postoperative nausea and vomiting: IV

- **Prevention, either alone or in combination with another antiemetic**: 5 mg as a single intravenous dose infused over 1 to 2 minutes at the time of induction of anesthesia.
- **Treatment**: 10 mg as a single intravenous dose infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure)

PEDIATRICS

Safety and effectiveness have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

- No dosage adjustment is necessary in patients with mild to moderate renal impairment.
- Avoid BARHEMSYS in patients with severe renal impairment.

HEPATIC IMPAIRMENT

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None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 5 mg/2 mL (2.5 mg/mL) in a single-dose vial.