Barhemsys®
(amisulpride) injection 2.5mg/mL

QT Prolongation Data

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.

acacia pharma

QT Prolongation Data

Barhemsys (amisulpride) injection 2.5mg/mL

Cardiac electrophysiology

Understanding and Evaluating QT Prolongation

Some antiemetics carry a risk for QT prolongation.[1] While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic risk, in general, there is a qualitative relationship between QT prolongation and the risk of torsades de pointes, especially for drugs that cause substantial prolongation of the QT interval.[2]

Many other drugs, including cardioactive drugs, and health conditions can induce QT prolongation. Both hypokalemia and hypocalcemia can prolong phase 2 and phase 3 of the action potential and prolong the QT interval.[3] Another important problem in the measurement of the QT/QTc interval is its intrinsic variability. This variability results from many factors, including activity level, postural changes, circadian patterns, and food ingestion.[2] American Heart Association guidelines emphasize that the presence of QT prolongation in an electrocardiogram (ECG) report should call for a careful clinical evaluation of possible causes.[3]

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommends categorical analyses on outliers. In clinical trials, a prolongation of QTc during therapy >500 milliseconds or a >60 milliseconds increase from baseline is considered a threshold of particular concern.[2]

BARHEMSYS QT Prolongation

The hERG channel is a voltage-gated potassium channel playing an essential role in the normal electrical activity of the heart. Mutations in the *HERG* gene and hERG channel blockage by small molecules have been associated with increased risk of QT prolongation.[4] Amisulpride binds relatively weakly to the hERG channel, with a half-maximal inhibitory concentration (IC_{50}) in the range 44-97 µM.[5]

BARHEMSYS causes dose- and concentration-dependent prolongation of the QT interval. The recommended dosage is 5 or 10 mg as a single IV dose infused over 1 to 2 minutes. Avoid BARHEMSYS in patients with congenital long QT syndrome and in patients taking droperidol. ECG monitoring is recommended in patients with pre-existing 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.[6]

In a thorough QT (TQT) study involving 40 healthy Caucasian and Japanese subjects, the maximum mean difference (95% upper confidence bound) in QTcF from placebo after baseline-correction (ΔΔQTcF) was 5.0 (7.1) milliseconds after a 2-minute IV infusion of BARHEMSYS 5 mg and 23.4 (25.5) milliseconds after an 8-minute IV infusion of amisulpride 40 mg.[6,7] A positive control of oral moxifloxacin adequately demonstrated assay sensitivity in line with international regulatory guidance.[2] A significant exposure-response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, BARHEMSYS 10 mg infused intravenously over 1 minute has a **maximal predicted** (95% upper prediction interval) ΔΔQTcF of 13.4 (15.1) milliseconds.[6,7]

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.[5]

Number of Subjects With QTcF Values Exceeding Absolute Threshold or Change Threshold[5]

	BARHEMSYS 5 mg (N=38)	Amisulpride 40 mg (N=38)	Moxifloxacin 400 mg (N=38)
Absolute threshold			
>450 msec to ≤480 msec	0	4	3
>480 msec	0	0	0
Change from baseline threshold			
>30 msec to ≤60 msec	0	5	0
>60 msec	0	0	0

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

acacia pharma

Barhemsys® (amisulpride) injection 2.5mg/mL

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

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.

Renal Impairment

Avoid BARHEMSYS in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2). 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 m^2).

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.

BAR HCP ISI 02/2020

References: 1. Gan TJ, Belani KG, Bergese S, et al. *Anesth Analg.* 2020;131(2):411-448. **2.** ICH of Technical Requirements for Pharmaceuticals for Human Use Topic E14. 2005. https://database.ich.org/sites/default/files/E14_Guideline.pdf. Accessed July 27, 2020. **3.** Rautaharju PM, Surawicz B, Gettes LS. *Circulation.* 2009;119(10):e241-e250. **4.** Sanguinetti MC, Tristani-Firouzi M. *Nature.* 2006;440(7083):463-469. **5.** Data on File. Acacia Pharma Inc. **6.** BARHEMSYS [Prescribing Information], Indianapolis, IN. Acacia Pharma; 2020. **7.** Taubel J, Ferber G, Fox G, et al. *Br J Clin Pharmacol.* 2017;83:339-348.

acacia pharma