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NCCN Guidelines Panel: Antiemesis

On behalf of Heron Therapeutics, Inc., and in anticipation of approval by the FDA for sales and marketing in the United States, I respectfully request a review of data supporting the inclusion of granisetron Injection, extended release (granisetron Inj. ER) in the Antiemesis Guidelines. If approved by the FDA we hope that granisetron Inj. ER will be included in the 2016 NCCN Antiemesis Guidelines update.

Specific Changes:

1. Recommend granisetron Inj. ER in combination with a neurokinin-1 (NK1) antagonist and dexamethasone, prior to high-emetogenic-risk intravenous chemotherapy (HEC) for prevention of acute and delayed emesis.
2. Recommend granisetron Inj. ER, in combination with dexamethasone, prior to moderate-emetogenic-risk intravenous chemotherapy (MEC) for prevention of acute and delayed emesis.

FDA Clearance: The NDA was submitted to the FDA on July 16, 2015, with an expected 6-month review period and a PDUFA date of January 17, 2016.[1]

Rationale: Granisetron Inj. ER is an extended-release polymer-based formulation designed to sustain granisetron exposure beyond that achieved with intravenous administration of 5-HT3 antagonists. A single subcutaneous dose of granisetron Inj. ER delivers therapeutic levels of granisetron for ≥5 days.[2] Two phase III studies support the efficacy and safety of granisetron Inj. ER[3-5]; further supportive data come from two phase II studies[6] and six phase I studies.[2,7] Over 2400 individuals were included in these trials.

The phase III MAGIC trial compared granisetron Inj. ER with standard-of-care ondansetron, each as part of a 3-drug regimen per NCCN guidelines (5-HT3 antagonist + NK1 antagonist + dexamethasone, D1; oral dexamethasone, D2-4) for prevention of nausea and vomiting (N/V) associated with HEC (defined by ASCO 2011 criteria). In this multicenter, randomized, double-blind trial, granisetron Inj. ER significantly increased delayed-phase complete response (CR) versus ondansetron (14.2% relative improvement) and demonstrated numerical superiority in complete control (Table). In addition, fewer rescue medications were used in the delayed phase (P = .013) and overall (P = .038), and self-reported patient satisfaction in the delayed phase was higher (P = .040). A post hoc analysis indicated granisetron Inj. ER was associated with less frequent nausea in the delayed (P = .032) and overall phases (P = .048).[5,8,9]

In a previous Heron-sponsored phase III trial, granisetron Inj. ER was non-inferior to palonosetron, each as part of a 2-drug regimen per NCCN guidelines at that time (5-HT3 antagonist + dexamethasone), for prevention of HEC- or MEC-associated N/V. All patients received dexamethasone as appropriate based on emetogenic risk.[3,4] CR rates were maintained over multiple cycles of treatment. In addition, a failure to respond to palonosetron in a small subset in cycle 1 did not preclude successful prevention of N/V with granisetron Inj. ER in subsequent cycles.[3]

In both of Heron's phase III trials, the overall incidence of adverse events (AEs) was similar between treatment arms and was consistent with previous reports in patients who received granisetron, palonosetron, or ondansetron. The most common AEs were constipation, fatigue, headache, and injection site reactions (ISRs).[3-5] The majority of ISRs were classified as mild to moderate in severity (no grade 4) based on size/appearance rather than functional impairment, and resolved during the study. Granisetron Inj. ER is not associated with QTcF interval prolongation or other changes in electrocardiogram intervals.[7]

In summary, granisetron Inj. ER is the first and only 5-HT3 antagonist to demonstrate superiority in a phase III, 3-drug versus 3-drug regimen efficacy trial for the prevention of N/V in patients receiving HEC, including adriamycin/cyclophosphamide (AC)- and cisplatin-based regimens. Notably, a recent phase III trial showed that palonosetron administered at 3 times the approved dose (0.75 mg) was not superior to oral granisetron for prevention of acute and delayed AC-associated N/V (Matsumoto K, et al. *J Clin Oncol.* 2015;33:abstr 9598). Granisetron Inj. ER is also the only extended-release 5HT3 antagonist studied in both acute and delayed N/V. Based on this highest level of evidence, we respectfully request that granisetron Inj. ER be considered for Category 1 preferred status for prevention of N/V in patients undergoing treatment with HEC. Based on the non-inferiority of granisetron Inj. ER to palonosetron for prevention of N/V associated with MEC in multiple tumor types, we respectfully request that the Review Panel also consider granisetron Inj. ER as a Category 1 preferred agent for prevention of N/V in patients undergoing treatment with MEC.

	Delayed			**Overall**		
	Granisetron Inj. ER n=450	Ondansetron n=452	*P*	Granisetron Inj. ER n=450	Ondansetron n=452	*P*
CR, %	64.7	56.6	**.014**	58.4	52.9	.092
CC, %	60.7	53.1	**.022***	54.7	49.6	.123*

CC: complete control, defined as CR with no more than mild nausea. CR: complete response, defined as no emetic episodes (vomiting or retching) and no use of rescue medications. **P* value unadjusted for type 1 error.

<u>The following publications are submitted in support of the requested changes:</u>

1. Food and Drug Administration, Department of Health and Human Services. NDA Acknowledgment: NDA 22445. September 11, 2015.
2. Ottoboni T, et al. *J Exp Pharmacol.* 2014;6:15-21.
3. Boccia R, et al. *J Community Support Oncol.* 2015;13:38-46.
4. Raftopoulos H, et al. *Support Care Cancer.* 2015;23:723-732.
5. Schnadig I, et al. In preparation, 2015.
6. Gabrail N, et al. *Cancer Manag Res.* 2015;7:83-92.
7. Mason JW, et al. *Cancer Manag Res.* 2014;6:181-190.
8. Schnadig I, et al. ASCO Breast Cancer Symposium 2015. Abstract 68.
9. Schnadig I, et al. ASCO Breast Cancer Symposium 2015. Oral presentation.