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#### **NCCN Guidelines Panel: Antiemesis**

On behalf of Heron Therapeutics, Inc., I respectfully request the NCCN Antiemesis Guideline Panel to consider the enclosed data and information to expand the current recommendations for SUSTOL® (granisetron) extended-release injection as the preferred 5-HT3 receptor antagonist (RA) for highly emetogenic chemotherapy (HEC), and for use with additional emetogenic chemotherapy regimens for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with both the initial and repeat courses of therapy.

Specific Changes: The following changes are requested:

1. Recommend SUSTOL as a preferred 5-HT3 RA, in combination with a neurokinin-1 (NK1) RA and dexamethasone, prior to intravenous (IV) HEC for prevention of acute and delayed CINV; (*AE-5, please specify Granisetron 10 mg SQ as preferred under all 5-HT3 RA listings on page AE-5*);
2. Recommend SUSTOL for use as a 5-HT3 RA prior to low emetic risk chemotherapy (LEC) for prevention of acute and delayed CINV; (*AE-8, please add to listings of 5-HT3 RA*);
3. Recommend SUSTOL as 5-HT3 RA prior to oral chemotherapy (HEC, moderately emetogenic chemotherapy [MEC], LEC) for prevention of acute and delayed CINV. (*AE-9, please add to listings for 5-HT3 RA for High, Moderate and Low*);
4. Per NCCN Guideline page AE-A (2 of 2), please specify the appropriate indication for “Managing Multiday Emetogenic Chemotherapy Regimens” for SUSTOL in the NCCN/Drugs/Biologics Compendium.

FDA Clearance: On 8/9/16, the FDA approved SUSTOL (1) for use in combination with other antiemetics for the prevention of acute and delayed CINV associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide (AC) combination regimens.

#### Rationale:

*The rationale for the specific change requests proceeds from available data, recommendations and information from authoritative sources such as the published literature, NCCN, FDA and ASCO and the interpretation of same through NCCN Panel expert judgment to meet patient needs. The NCCN alludes to the need for expert judgment (AE-A 2 of 2, footnote 1) in the Guideline as it acknowledges that “evidence is lacking to support every clinical scenario”. The recent ASCO Guideline update (JCO online, July 31, 2017) acknowledged that in “selected cases where evidence was lacking -but there was a high level of agreement among Expert Panel members- informal consensus was used”. (2) The following outlines specific data, information and clinical logic supporting the four requested changes above.*

#### **1. Recommend SUSTOL as a “preferred” 5-HT3 antagonist for prevention of acute and delayed CINV with HEC:**

- SUSTOL is the first 5-HT3 antagonist to demonstrate superiority in a randomized phase 3, 3-drug versus 3-drug regimen trial for the prevention of delayed CINV in patients receiving HEC, including AC and cisplatin-based regimens. SUSTOL (in combination) has demonstrated superior control of delayed phase CINV following HEC vs the standard 3-drug regimen of ondansetron, fosaprepitant, and dexamethasone. (3)
- In the phase 3, multicenter, randomized, double-blind MAGIC trial (3), SUSTOL achieved a delayed phase complete response (CR) (primary endpoint), defined as no emesis and no rescue medications, of 64.7% versus 56.6% ( $p = .014$ ) for ondansetron equating to a 14.2% relative improvement. In addition, fewer rescue medications were used in the delayed ( $p = .013$ ) and overall ( $p = .038$ ) phases, and self-reported patient satisfaction in the delayed phase was higher ( $p = .040$ ) with SUSTOL. Within the cisplatin stratum (28% of study population), delayed-phase CR rates were 65.3% with the SUSTOL regimen and 54.7% with the ondansetron regimen. A post hoc analysis indicated SUSTOL was associated with less frequent nausea in the delayed ( $p = .032$ ) and overall phases ( $p = .048$ ). This decrease of nausea frequency is notable since less rescue medications were used during this time-period. This study highlighted the superior efficacy of SUSTOL thus favorably distinguishing SUSTOL which supports a preferred status.
- Sustol was demonstrated (4) to have excellent antiemetic activity in patients ( $n=34$ ) after palonosetron failure in HEC as 45.5% of the HEC delayed failures achieved a CR with SUSTOL and 58.3% of the HEC failures in the acute phase achieved CR with SUSTOL in their second cycle of chemotherapy.
- A recent trial (5) showed that in a 3-drug antiemetic regimen, palonosetron at 3 times (0.75 mg) the approved dose was not superior to oral granisetron for prevention of acute and delayed AC-associated CINV.

- Criticisms of the palonosetron 2-drug comparison study in acute and delayed HEC vs granisetron (IV) are delineated on NCCN page MS-18 left column. Conversely, the SUSTOL MAGIC study cited was a phase 3, multicenter, randomized, double blind trial where each 3-agent combination was dosed appropriately in both the experimental and control arms. The MAGIC study demonstrated superiority for the SUSTOL 3-drug regimen over the ondansetron 3-drug regimen in prevention of the delayed phase of CINV in HEC.
- SUSTOL has been shown to sustain therapeutic levels of granisetron for  $\geq 5$  days beyond the durations seen with other 5-HT3 antagonists. (6,7) As such, SUSTOL therapeutic levels clearly are maintained and far exceed the duration of therapeutic prophylactic coverage specified by NCCN for both MEC (2 days) and HEC (3 days) patients. (NCCN page MS-16).
- SUSTOL is the only 5-HT3 antagonist with an FDA approved indication to prevent delayed nausea and vomiting in HEC chemotherapies (anthracyclines and cyclophosphamide). Palonosetron is FDA-approved only for prevention of the acute phase of HEC.
- Unlike 1st generation 5-HT3 RAs, SUSTOL was not required by the FDA to carry a label warning about prolongation of the QT interval due to the lack of association between SUSTOL and QTcF interval prolongation. (8)

**2. Recommend SUSTOL for use as a 5-HT3 antagonist prior to LEC for prevention of acute and delayed CINV:**

- Updated ASCO Guideline lists granisetron SQ (SUSTOL) as an option for LEC (Table 3, page 10) with the explanation on first column page 11 as follows: “The decision by the Expert Panel to add a 5-HT3 receptor antagonist as an option for patients who are treated with low-emetic-risk antineoplastic agents is based on the fact that these agents are an effective and safe standard to prevent emesis caused by high- and moderate-risk anticancer therapies and meet the needs of clinicians who have concerns about the adverse effects of corticosteroids.”
- ASCO, in its tables for HEC, MEC and LEC, always has three granisetron (oral, transdermal, and SQ extended release) formulations listed, including granisetron SQ (SUSTOL) for LEC.

**3. Recommend SUSTOL as a 5-HT3 RA prior to oral chemotherapy (HEC, MEC or LEC) for prevention of acute and delayed CINV.**

- The FDA labeled indication covers uses prior to both oral and IV chemotherapy.
- In ASCO’s recently updated Guideline, ASCO does not distinguish between CINV associated with IV vs oral antineoplastic agents. As such, SUSTOL is considered and listed as a therapeutic option for CINV associated with oral chemotherapy in addition to IV therapy.

**4. Per NCCN Guideline page AE-A (2 of 2), please specify the appropriate indication for “Managing Multiday Emetogenic Chemotherapy Regimens” for SUSTOL in the NCCN Drugs/Biologics Compendium.**

- The NCCN Drugs/Biologics Compendium is generally consistent with the NCCN Guidelines. As such, it is requested that the indication for managing multiday emetogenic chemotherapy regimens be specified in this Compendium.

*In summary*, based on this highest level of evidence, we respectfully request that SUSTOL be considered for preferred status for prevention of CINV in patients undergoing treatment with HEC. Further, we request that NCCN Panel experts consider specific recommendations for the use of SUSTOL as a therapeutic option for LEC and as a therapeutic option for oral chemotherapy categorized as HEC, MEC or LEC. Finally, we request that the indication for “Managing Multiday Emetogenic Chemotherapy Regimens” be added to the NCCN Drugs/Biologics Compendium for SUSTOL. Thank you for time and consideration in this matter.



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References (Enclosures 8)

1. Food and Drug Administration; Approval Notice and Prescribing Information. August 9, 2016.
2. Hesketh P et al. *JCO*. 2017; 35: 1-22.
3. Schnadig I et al. *Future Oncol* 2016; 12:1469-81
4. Arevalo-Araujo R et al. *JCO* 2013; 31: abstr 20569.
5. Matsumoto K et al. *JCO*. 2015; 33: abstr 9598.
6. Ottoboni T et al. *J. Exp. Pharmacol.* 2014; 6:15-21.
7. Gabrail N et al. *Cancer Manag Res.* 2015;7: 83-92.
8. Mason J et al. *Cancer Manag Res*, 2014;6:181-190.