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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 for SUSTOL® (granisetron) extended-release injection, for subcutaneous use in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with both the initial and repeat courses of therapy, including, but not limited, to highly emetogenic chemotherapy (HEC).

Specific Changes:
The following changes are requested:

1. Recommend SUSTOL as a preferred 5-HT3 antagonist, in combination with a neurokinin-1 (NK1) antagonist and dexamethasone, prior to intravenous (IV) HEC for prevention of acute and delayed CINV;
2. Recommend SUSTOL as a preferred 5-HT3 antagonist (parity with palonosetron), in combination with dexamethasone with or without a NK1 antagonist prior to IV moderately emetogenic chemotherapy (MEC) for prevention of CINV;
3. Recommend SUSTOL as a preferred 5-HT3 antagonist prior to oral chemotherapy with either HEC or MEC for prevention of acute and delayed CINV.

FDA Clearance: On August 9, 2016, the FDA approved SUSTOL 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.[1]

Rationale: *SUSTOL is the first and only 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.*[2]

Despite advances, poor CINV control persists, particularly in the delayed phase with HEC. As specified in the NCCN Guideline (AE-1), patients who are receiving HEC or MEC require effective protection with an antiemetic *through the full time period of that risk*. SUSTOL, an injectable sustained release formulation of granisetron, has been shown to sustain therapeutic levels of granisetron for ≥5 days,[3] beyond the duration seen with all other formulations of 5HT-3 antagonists. SUSTOL (in combination) has demonstrated superior control of delayed phase CINV following HEC vs the standard 3-drug regimen of ondansetron, fosaprepitant, and dexamethasone.[2] It is noteworthy that the phase 3 Modified Absorption of Granisetron In the prevention of Chemotherapy-induced nausea and vomiting (MAGIC) trial, represents the first pivotal phase 3 efficacy trial in HEC to use guideline recommended 3-drug regimens in both treatment arms.

In the phase 3, multicenter, randomized, double-blind MAGIC trial, 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.[2] 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. The authors concluded that the MAGIC study was the first Phase 3 study to demonstrate superiority of a 5HT-3 antagonist (i.e., SUSTOL) over another in delayed phase CINV following HEC in the presence of an NK-1 antagonist and dexamethasone. This study highlights the superior efficacy of SUSTOL and favorably distinguishes SUSTOL's efficacy from that of other 5HT-3 antagonists, which strongly supports preferred status.

In the previous phase 3 trial, SUSTOL 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 CINV.[4] All patients received dexamethasone as appropriate based on emetogenic risk. CR rates were maintained over multiple cycles of treatment.[5] In addition, a failure to respond to palonosetron in a small subset in cycle 1 did not preclude successful prevention of CINV with SUSTOL in subsequent cycles.

Further, the results of another clinical trial provided no evidence that palonosetron is more effective in controlling delayed nausea than even the first generation granisetron.[6] Another, recent trial also showed that palonosetron at 3 times the approved dose (0.75 mg) was not superior to oral granisetron for prevention of acute and delayed AC-associated CINV.[7]

In the phase 3 SUSTOL clinical 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.[2,4] The most common AEs were constipation, fatigue, headache, and injection site reactions (ISRs). 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. In clinical trials SUSTOL was not associated with QTcF interval prolongation or other cardiac toxicities.[8,9]

*In summary, SUSTOL is the first and only 5-HT3 antagonist to demonstrate superiority in a phase 3, 3-drug versus 3-drug regimen trial for the prevention of CINV in patients receiving HEC, including AC and cisplatin-based regimens.[2]* SUSTOL is also the only extended-release 5HT3 antagonist studied in both acute and delayed CINV. Based on this highest level of evidence, we respectfully request that SUSTOL be considered for Category 1 preferred status for prevention of CINV in patients undergoing treatment with HEC. Based on the non-inferiority of SUSTOL to palonosetron for prevention of CINV associated with MEC, we respectfully request that the Guideline Panel also consider SUSTOL as a Category 1 preferred agent for prevention of CINV in patients treated with MEC.

Respectfully Submitted,

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References (Enclosures 9)

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