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ProStrakan

Date: September 25, 2014

Submission Request c/o Joan McClure
National Comprehensive Cancer Network
500 Old York Road, Suite 250
Jenkintown, PA 19046

RE: Evidence in Support of Additional Language Regarding the Approved Use of Transdermal Granisetron for the Prevention of Emesis in Multiday Emetogenic Chemotherapy Regimens

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Date of request: September 25, 2014
NCCN Guidelines Panel: Antiemesis

Dear Guidelines Panel,

On behalf of ProStrakan Group, I respectfully request the NCCN Antiemesis Guidelines Panel review the enclosed information in support of amending the guidelines to accurately reflect all approved agents and routes of administration of serotonin antagonists for the prevention of nausea and vomiting associated with multiday chemotherapy regimens.

Specific changes: As a result of the information provided in this letter and the accompanying documentation, we are requesting a change to the Principles of Managing Multiday Emetogenic Chemotherapy Regimens section of the guidelines (Section AE-A).

We are also requesting an expansion of the discussion section to include information regarding the approved use of transdermal granisetron in multiday chemotherapy regimens (Section MS-16).

FDA status: Sancuso® (Granisetron Transdermal System) is approved in the United States for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days' duration.(1)

Rationale for recommended changes: The granisetron transdermal patch is currently listed in Version 2.2104 of the NCCN Antiemesis guidelines as a seratonin receptor antagonist for highly emetogenic intravenous chemotherapy (Section AE-2) and for moderately emetogenic intravenous chemotherapy (Section AE-3) emesis prevention. The patch is correctly referenced as one of several dosing options for granisetron. (2)

However, under the Principles of Managing Multiday Emetogenic Chemotherapy Regimens (Section AE-A), transdermal administration of granisetron is not cited as an option despite its evidence-based

approval and proven efficacy in patients receiving multiday chemotherapy regimens. In contrast, the safety of repeated dosing of palonosetron is discussed as "likely to be safe" and its efficacy "not yet known" but repeated palonosetron dosing receives mention in this section of the guidance. (2)

In order to attain fair balance we respectfully request transdermal granisetron be added to the guidelines in both Section AE-A and the accompanying Discussion (refer to Appendix A: Table of Proposed Changes) to accurately reflect currently approved serotonin receptor antagonist options in multiday chemotherapy emesis prevention.

Supporting literature: This request to amend the NCCN treatment guidelines to include discussion of transdermal granisetron in managing multiday emetogenic chemotherapy regimens is based on data from one key Phase III randomized, double-blind, placebo-controlled study, upon which Sancuso's approval was based. (3) Briefly, this study compared the efficacy of the granisetron transdermal patch with oral granisetron (2 mg) for preventing chemotherapy-induced nausea and vomiting in 641 patients receiving moderately emetogenic and highly emetogenic multi-day chemotherapy. Sixty-eight percent of patients received chemotherapy regimens of ≤ 3 days and 32% received regimens of 4-5 days. The majority of transdermal granisetron patients (71%) were given highly-emetogenic, cisplatin-based regimens. The transdermal granisetron patch or placebo patch was applied 24–48 hours prior to the initiation of chemotherapy and remained in place for a 7-day treatment period. The primary endpoint was complete control of nausea and vomiting (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final chemotherapy administration. (3)

Complete control was achieved by 60% of patients in the transdermal granisetron group. Local skin tolerability of the transdermal patch was good, with only one reported case of application site pruritus related to patch use. The granisetron patch was well tolerated, with the most common adverse event being constipation in 6.6% of patients. (3)

We appreciate the opportunity to provide this additional information for consideration by the NCCN Antiemesis Panel. If you have any questions or require additional information, please do not hesitate to contact me at 908-432-7271 or via e-mail at deborah.braccia@prostrakan.com. Thank you for your time and consideration.

Sincerely,

Deborah Braccia, PhD, MPA

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1. Sancuso (Granisetron Trandermal System) [package insert] Bridgewater, N.J. Prostrakan, Inc. 2014.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Antiemesis Version 2.2014. Available at http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed September 22, 2014.
3. Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM, Sancuso Study G**.** Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. Support Care Cancer. 2011;19(10):1609-17.

Enclosures:
Table of proposed changes
Sanscuso Package Insert
Boccia manuscript

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APPENDIX A: Table of Proposed Changes to the NCCN Clinical Practice Guidelines in Oncology: Antiemesis Version 2.2014

Section	Current Text; Version 2.2014	Proposed Changes
AE-5	"Practical issues also need to be considered when designing the antiemetic regimen, taking into account the administration setting (eg. inpatient versus outpatient), preferred route of administration (IV versus oral), duration of action of the serotonin antagonist……."	"Practical issues also need to be considered when designing the antiemetic regimen, taking into account the administration setting (eg. inpatient versus outpatient), preferred route of administration (IV, *oral, or transdermal*), duration of action of the serotonin antagonist……"
AE-5	"A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. The frequency of repeated administration of the serotonin agonist depends on the agent chosen."	"A serotonin antagonist should be administered prior to the first (and subsequent) doses of moderately or highly emetogenic chemotherapy. The frequency *or need for* repeated administration of the serotonin antagonist depends on the *chosen agent and its mode of administration (IV, oral or transdermal).*
MS-16	A 5-HT3 receptor antagonist should be administered each day before the first dose of moderately or highly emetogenic chemotherapy. Intravenous palonosetron may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. [164,165] Repeat dosing of palonosetron…….	A 5-HT3 receptor antagonist should be administered each day before the first dose of moderately or highly emetogenic chemotherapy. Intravenous palonosetron or *the transdermal granisetron patch* may be used before the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT3 receptor antagonists. [164,165] *The transdermal patch has been shown to be effective at controlling emesis for up to 5 consecutive days of moderately or highly emetogenic chemotherapy. [Boccia ref]. One patch can be worn for a maximum of 7 days. [Boccia ref]* Repeat dosing of palonosetron…….

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