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NCCN Guidelines Panel: Antiemesis

RE: Suggested changes and updates to selected portions of the NCCN Antiemesis Guidelines that pertain to published clinical data for AKYNZEO® (netupitant/palonosetron) capsules and AKYNZEO® (fosnetupitant/palonosetron) injection (each of which is also referred to by the acronym, NEPA).

On behalf of Helsinn Therapeutics (U.S.), Inc. and Helsinn Healthcare SA, I respectfully request that the NCCN Antiemesis Guidelines Panel review the following information and related published clinical studies that support the following series of suggested specific changes to the Antiemesis Guidelines.

Specific Change #1

Modify the Antiemesis Guidelines to state that dexamethasone-sparing strategies – typically the limitation to one dose of dexamethasone on day 1 only – can also be used with cisplatin regimens when NEPA is administered concomitantly.

Applicable locations in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: (i) Page AE-5A – footnote "u"; (ii) Page AE-A, 1 of 3 – section on Corticosteroids / Dexamethasone-sparing strategies (third bullet), first sub-bullet; (iii) Page MS-16 – second full paragraph (which includes a discussion of dexamethasone-sparing)

FDA approval status of this use: AKYNZEO® (netupitant/palonosetron) capsules and AKYNZEO® (fosnetupitant/palonosetron) injection are each FDA approved for use in the prevention of CINV in patients receiving highly emetogenic chemotherapy, including cisplatin. The current FDA approved dose of dexamethasone to be used in conjunction with AKYNZEO® is 12 mg on day 1 followed by dexamethasone 8 mg daily on days 2, 3, and 4. The "dexamethasone-sparing" dosage regimen described in this change request – dexamethasone 12 mg on day 1 only – is not an FDA-approved dose for use with AKYNZEO®.

Rationale for this proposed change: As the NCCN Antiemesis Guidelines currently state, for a variety of clinical reasons, it may be desired to administer dexamethasone on day 1 only for selected patients

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receiving emetogenic chemotherapy. Heretofore, such "dexamethasone-sparing" antiemetic regimens have been shown to be adequately effective only for non-cisplatin HEC. A recently-published randomized multicenter clinical study involving 226 high-dose cisplatin patients (Celio, et al., 2021) documented that when given in conjunction with NEPA, a single 12 mg dose of dexamethasone on day 1 only provided as much antiemetic efficacy as the standard dexamethasone dose of 12 mg on day 1 (also with NEPA), followed by dexamethasone 8 mg daily on days 2, 3, and 4. Accordingly, when NEPA is used for the recommended 5-HT_3 receptor antagonist ($5HT_3RA$) and NK-1 receptor antagonist (NK1RA) components of the antiemetic regimen, a single dose of dexamethasone 12 mg on day 1 can be used effectively for cisplatin patients who would benefit from lower doses of dexamethasone.

Supporting literature: Celio L, Cortinovis D, Cogoni AA, et al. Dexamethasone-sparing regimens with oral NEPA for the prevention of emesis caused by high-dose cisplatin: A randomized non-inferiority study. *The Oncologist* 2021 (e-pub ahead of print) http://dx.doi.org/10.1002/onco.13851. [see PDF attachment]

Specific Change #2

Modify the Antiemesis Guidelines to acknowledge that multiple doses of NEPA (on days 1, 3, and 5) have been shown to be effective at preventing CINV in patients receiving multiday highly emetogenic chemotherapy prior to hematopoietic stem cell transplant.

Applicable locations in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: (i) Page AE-A, 2 of 3 – (NK1RA section) – (a) add a new sub-bullet stating that data from a multicenter phase II study supports multiday dosing of NEPA in association with BEAM/FEAM conditioning regimens prior to stem cell transplant; (b) modify the current sub-bullet 5 to remove netupitant from the statement, "Studies investigating repeat dosing . . . are not available."; (ii) Page AE-A, 3 of 3 – add the Di Renzo, et al. study to the list of cited references ; (iii) Page MS-27 – [within the section on NK1RAs (that begins on page MS-26); in the last paragraph (that begins with "NK1")]– (a) prior to the last sentence, add text summarizing the data from the Di Renzo, et al. study supporting the use of multiday dosing of NEPA in association with BEAM/FEAM conditioning regimens prior to stem cell transplant; (b) modify the current last sentence in this paragraph (just prior to the Summary) by removing "NEPA" from the statement that "Data are not available for repeat dosing of fosaprepitant, aprepitant injectable emulsion, NEPA, or oral rolapitant."

FDA approval status of this use: AKYNZEO® (netupitant/palonosetron) capsules and AKYNZEO® (fosnetupitant/palonosetron) injection are not FDA approved for multiple dose use in association with multiday emetogenic chemotherapy regimens.

Rationale for this proposed change: The multicenter phase II study by Di Renzo, et al. (2020) involved 70 patients who received multiday highly and moderately emetogenic BEAM or FEAM conditioning chemotherapy regimens prior to stem cell transplantation for non-Hodgkin's lymphoma. NEPA was given on days 1, 3, and 5 during the conditioning chemotherapy. (Dexamethasone was not included in the antiemetic regimen, as per physician decision in this trial.) The assessment period totaled fifteen days: the conditioning period (acute phase, days 1-6; delayed phase, days 7-8; overall phase, days 0-8) and the follow-up period (days 9-15). A very high percentage of patients achieved Complete Response,

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Complete Control, and experienced minimal or no nausea in the acute, delayed, overall, and follow-up time periods. Side effects noted were few in number and of minor severity. This study is the first to document the efficacy and safety of multiple dosing of NEPA in patients receiving multiday highly emetogenic chemotherapy regimens.

Supporting literature:
Di Renzo N, Musso M, Scimè R, et al. Efficacy and safety of multiple doses of NEPA without dexamethasone in preventing nausea and vomiting induced by multiple-day and high-dose chemotherapy in patients with non-Hodgkin's lymphoma undergoing autologous hematopoietic stem cell transplantation: a phase IIa, multicenter study. *Bone Marrow Transplantation* 2020;55:2114-20. [see PDF attachment]

Specific Change #3

Modify the Antiemesis Guidelines by adding to the section describing NEPA an additional paragraph summarizing the two comparative safety studies performed with NEPA injection and NEPA capsules. Note that one study involved cisplatin patients and the other study involved AC patients. The results of both studies documented no safety concerns and no injection site reactions associated with injectable NEPA.

Applicable location in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: Page MS-13 – add the requested safety study information as a new fourth paragraph in the NEPA section.

FDA approval status of this change: No information pertaining to the two Schwartzberg, et al. NEPA safety studies is included in the Akynzeo® product labeling.

Rationale for this proposed change: The two Schwartzberg, et al. safety studies comparing NEPA injection to NEPA capsules are important to mention as both studies report no safety issues associated with the use of NEPA injection in patients receiving HEC.

Supporting literature: (i) Schwartzberg L, Roeland E, Andric Z, et al. Phase III safety study of intravenous NEPA: a novel fixed antiemetic combination of fosnetupitant and palonosetron in patients receiving highly emetogenic chemotherapy. *Ann Oncol* 2018;29:1535-40; (ii) Schwartzberg L, Navari RM, Clark-Snow R, et al. Phase IIIb safety and efficacy of NEPA for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with breast cancer receiving initial and repeat cycles of anthracycline and cyclophosphamide (AC) chemotherapy. *The Oncologist* 2020;25:e589-e597. [see PDF attachments]

Specific Change #4

Modify the Antiemesis Guidelines by adding to the descriptive information about fosnetupitant/palonosetron injection that the product is formulated to minimize any risks of infusion site reactions or hypersensitivity reactions and as such, it contains no emulsifiers, surfactants, or stabilizers such as polysorbate 80, soy, lecithin, or egg albumin.

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Applicable location in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: Page MS-13 – add this formulation information to the first paragraph in the NEPA section.

FDA approval status of this change: The formulation of AKYNZEO® injection, including inactive ingredients, is part of the FDA-approved product labeling for AKYNZEO® (section 11).

Rationale for this proposed change: The formulation of NEPA injection was developed intentionally to not require any emulsifiers, surfactants, or stabilizers since inactive ingredients of this nature that are present in other injectable NK1RAs are thought to be associated with the known risks of infusion site reactions, as reported when using fosprepitant injection or aprepitant injection.

Supporting literature: AKYNZEO® [Package Insert (section 11)], Iselin, NJ: Helsinn Therapeutics, (U.S.), Inc. June 2021. [see PDF attachment]

Specific Change #5

Modify the Antiemesis Guidelines by adding further detail to the summary of the Zhang, et al. study to note that the proportion of patients experiencing emesis and/or use of rescue medication on day 5 was significantly smaller among the patients who received NEPA than among the patients who received granisetron/aprepitant.

Applicable location in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: Page MS-13 – add this additional detail to paragraph 3 in the NEPA section.

FDA approval status of this change: No information pertaining to the Zhang, et al. study is included in the Akynzeo® product labeling.

Rationale for this proposed change: The Zhang, et al. study is one of the few published comparative trials of NEPA vs. another $5HT_3RA$/NK1RA combination. While the summary description currently present in the Antiemesis Guidelines is accurate, adding this additional finding from the study's results will provide a more complete picture of the study results.

Supporting literature: Zhang L, Lu S, Feng J, et al. A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy. *Ann Oncol* 2018;29:452-8. [see PDF attachment]

Specific Change #6

Modify the Antiemesis Guidelines by expanding with new comparative data the section focusing on decreasing delayed nausea. This section already states that data suggest that oral netupitant is effective at decreasing delayed nausea. The recently-published pooled analysis study by Navari, et al. adds helpful new comparative information reporting NEPA + dexamethasone achieves superior prevention of delayed nausea compared to aprepitant + any $5HT_3RA$ + dexamethasone.

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Applicable location in the NCCN Antiemesis Guidelines (version 1.2021) where this change should be made: Page MS-22 – modify the last paragraph in column 1 on this page to note the new comparative data from the Navari, et al. pooled analysis.

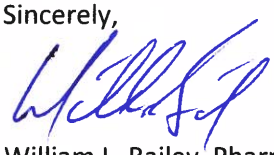
FDA approval status of this change: No information pertaining to the Navari, et al. pooled analysis is included in the Akynzeo® product labeling nor does the product labeling make any statement regarding the comparative efficacy of NEPA versus anti-emetic regimens containing aprepitant.

Rationale for this proposed change: The Navari, et al. pooled analysis involved three registrational clinical trials, each of similar design and patient populations. All patients received cisplatin. A total of 621 patients received NEPA + dexamethasone and 576 patients received aprepitant + dexamethasone + a $5HT_3RA$ (either ondansetron, granisetron, or palonosetron). Results of the pooled analysis provide confirmation of NEPA's usefulness in minimizing delayed emesis and delayed nausea. Importantly, the results also provide initial evidence that NEPA is superior to aprepitant-containing regimens in preventing both delayed nausea and delayed emesis. Furthermore, the pooled analysis results provide evidence that in the small proportion of patients who do experience breakthrough CINV (emesis and/or use of rescue medication) patients in the affected subset who received NEPA were more likely to experience such symptoms for only one or two days whereas patients in the affected subset who received an aprepitant-containing regimen were more likely to have breakthrough symptoms persist for three to five days.

Supporting literature: Navari RM, Binder G, Bonizzoni E., et al. Single-dose netupitant/palonosetron versus 3-day aprepitant for preventing chemotherapy-induced nausea and vomiting: a pooled analysis. *Future Oncology* 2021 (e-pub ahead of print) https://www.futuremedicine.com/doi/10.2217/fon-2021-0023. [see PDF attachment]

We thank the NCCN for the opportunity to submit these suggested changes and the NCCN Antiemesis Guidelines Panel for giving this information their careful attention as they update these important Guidelines.

Sincerely,



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Enclosures: PDFs of each of the supporting literature studies as well as of the AKYNZEO® product label