Submitted By:

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11/7/19

NCCN Guidelines Panel:

On behalf of TerSera Therapeutics, I respectfully request the *Management of Immunotherapy-Related Toxicities Panel* review the newly FDA-approved product called Quzyttir (cetirizine hydrochloride for injection), the first intravenous (IV) second-generation antihistamine, for inclusion in your guidelines. It is noted on the NCCN website your panel met on July 23, 2019. Quzyttir was approved on October 4, 2019, after the panel meeting. I respectfully request your panel review the following recommendations and enclosed data in light of this significant medical advancement over the only existing treatment option, a first-generation IV antihistamine, diphenhydramine.

Recommendation #1: On page ICI_INF-1:Management of Immune Checkpoint Inhibitor-Related Toxicities / Infusion-Related Reactions: For moderate infusion reactions in which infusion interruption is indicated, Footnote C mentions "antihistamines", but does not clarify IV versus oral antihistamines. Similarly, on page MS-16:Infusion reaction/NCCN recommendations, there is no clarification of IV versus oral antihistamines. With a recently approved second-generation IV antihistamine and the need to address such reactions quickly, clarifying the need for an IV formulation is important.

> Specific Change Recommended: On page ICI-INF-1, in Footnote C, change the word "antihistamines" to "IV antihistamines". On page MS-16, for moderate (G2) reactions, change the word "antihistamines" to "IV antihistamines".

Recommendation #2: On page ICI_INF-1 –Management of Immune Checkpoint Inhibitor-Related Toxicities / Infusion-Related Reactions: The last bullet in the mild or moderate management section states: "Consider premedication with acetaminophen and diphenhydramine for future infusions". For patients at high risk of infusion reaction, ensuring quick antihistamine levels at time of infusion is important. We are unclear if the current diphenhydramine recommendation is because it is the only IV antihistamine that has previously been available. As such, we would recommend a wording change.

> Specific Change Recommended: "Consider premedication with acetaminophen and an IV antihistamine for future infusions"

Recommendation #3: On page ICI_DERM-2- Management of Immune Checkpoint Inhibitor-Related Toxicities / Dermatological Adverse: For severe Pruritus, Footnote K mentions "Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE." Similarly, on page MS-18 - Management of Immune Checkpoint Inhibitor-Related Toxicities: Dermatological Toxicity/NCCN Recommendations, mentions "For severe pruritus, hold immunotherapy and obtain urgent dermatology consultation. In addition to antihistamines, oral or IV prednisone/methylprednisolone (0.5–1 mg/kg/day) should be administered." This is a severe condition where initial IV treatment would be beneficial. We recommend, similar to prednisone/methylprednisolone, the addition of IV antihistamines." As such, we would recommend a wording change.

> Specific Change Recommended: On page ICI_DERM-2 Footnote K and on page MS-18: change the word "antihistamines" to "IV antihistamines".

Supporting Clinical Data for Recommendation

FDA Clearance: Diphenhydramine[1] has been the only IV H1-antihistamine approved for use in this setting. Diphenhydramine is a first-generation antihistamine that is highly lipophilic and significantly crosses the blood blain barrier. This leads to multiple adverse events that include sedation, confusion, urinary retention, dry mouth and dry eyes. Cardiovascular events such as hypotension, extrasystoles, tachycardia and palpitations may also occur. These adverse events are more

pronounced in elderly patients.[2] These side effects complicate clinical management of patients requiring IV antihistamines. Additionally, due to the short half-life of diphenhydramine, the product has to be dosed 3 to 4 times a day as needed.

FDA-approved QUZYTTIR™, [3] (cetirizine hydrochloride injection), the first IV formulation of a second-generation antihistamine is indicated for the treatment of acute urticaria in adults and children 6 months of age and older. Quzyttir 10 mg is administered IV push over one to two minutes, has a Tmax of 1.8 minutes, half-life of 8 hours, and is dosed once every 24 hours as needed. It works primarily at the H1 receptor sites in the peripheral space with limited CNS penetration. Cetirizine has a well-established safety profile. Quzyttir demonstrated fewer side effects and less sedation than diphenhydramine. No overall differences were seen in safety in patients over 65 years of age versus those younger than 65 years of age treated with Quzyttir in the phase III clinical trial. This treatment provides an option for patients who need IV antihistamines for management of acute reactions due to immunotherapy.

Clinical trials supporting the safety and efficacy of QUZYTTIR™

- Two clinical studies were conducted to establish the efficacy and safety of QUZYTTIR™

  The first was a pilot study (ETTAU-02)[3,4] conducted in 33 patients. The study demonstrated that 10mg QUZYTTIR™, was similar to 50mg IV diphenhydramine in treating acute urticaria symptom score reductions (composite score and each individual symptom score, such as: pruritus and extent of urticaria/erythema at 1 or 2 hours post-injection and at discharge). There were no serious adverse events (SAEs) in either treatment arm. There were no drug-related adverse events (AEs) from the cetirizine HCl arm, but several drug-related AEs were recorded in patients in the diphenhydramine arm.

  The second study was a pivotal Phase 3 study (ETTAU-03) [3] in 262 patients that demonstrated similar results as in the pilot study (ETTAU-02). This study also demonstrated that 10mg QUZYTTIR™ is similar to 50mg IV diphenhydramine for the primary endpoint (2-hour patient-rated pruritus score change from baseline).[3,5] Key secondary endpoints (time spent in treatment center and percentage of patients returned to treatment center within 24 hours) were better with QUZYTTIR™ compared to IV diphenhydramine. Patients treated with QUZYTTIR™ had less sedation, reduced rescue-drug usage, and higher rate of effective treatment compared to IV diphenhydramine.[3-5]

Supporting References:

1. Diphenhydramine hydrochloride injection [package insert]. Franklin Lakes, NJ: BD Rx Inc.; 2012.
2. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694.
3. QUZYTTIR (cetirizine hydrochloride injection) [package insert]. Lake Forest, IL: TerSera Therapeutics LLC.; 2019.
4. Data on File. TerSera Therapeutics LLC.
5. Abella BS, Berger W, Blaiss M, et al. IV cetirizine versus IV diphenhydramine in treatment of acute urticaria. [Abstract 310]. *Ann Emerg Med*. 2019;74(4 suppl S1):e147.

Thank you in advance for your review of this information. Please do not hesitate to contact me via email or telephone with any questions you may have.

Best Regards,

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