



Submitted By:

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NCCN Guidelines Panel:

On behalf of TerSera Therapeutics LLC, I respectfully request panel review of data from a Phase 2 study of intravenous (IV) QUZYTIR (cetirizine hydrochloride for injection) versus IV diphenhydramine in the prevention of hypersensitivity infusion reactions in an oncology setting (NCT04189588) for inclusion in the *NCCN Older Adult Oncology* guidelines.¹ TerSera previously submitted a letter on September 11, 2020 (letter attachment) requesting the panel update the guidelines with information regarding QUZYTIR for the treatment of acute urticaria (PI, Abella).^{2,3} I was recently informed the panel would be updating the guidelines in late March and was asked to submit our most recent clinical trial data. TerSera's recommendations are below and I have enclosed the requested data for this advancement in patient care for IV H1-antihistamine therapies, where the sole option has previously been IV diphenhydramine.^{4,5}

Recommendation: Page OAO-I 2 of 5: MEDICATIONS COMMONLY USED FOR SUPPORTIVE CARE THAT ARE OF CONCERN IN OLDER PATIENTS: The recommendations state that first-generation H1 antihistamines should be used for supportive care only when convincing benefit exists, and that they are appropriate for acute treatment of severe allergic reactions (route of administration is not mentioned). The alternative options provided suggest the use of second-generation antihistamines to treat allergic reactions with no mention of the availability of an IV agent. With a recently approved second-generation IV H1-antihistamine, robust data from three head-to-head studies between IV cetirizine and IV diphenhydramine, and the clinical need to treat allergic reactions quickly, it is important to clarify the H1 antihistamine options in the guidelines, particularly an option that may have less side effects for elderly patients.

Specific Changes Recommended for Antihistamines:

1. On page OAO-I 2 of 5, in the recommendation section, consider changing the second bullet commenting on the appropriateness of using first-generation H1-antihistamines to "For acute treatment of severe allergic reactions, recommend a second-generation IV antihistamine (cetirizine)."
2. In the alternatives section, consider adding a bullet stating, "For preventing allergic reactions in the oncology setting, recommend a second-generation IV antihistamine (cetirizine)."

Clinical trials supporting the safety and efficacy of QUZYTIR

- Three separate head-to-head clinical trials have been conducted evaluating the safety and efficacy of IV cetirizine versus IV diphenhydramine (See Table 1 Below). The most recent study conducted was just accepted for presentation at the 38th Annual Miami Breast Conference on March 4, 2021.¹ This study was a Phase 2, double-blind, randomized controlled study evaluating the prevention of hypersensitivity infusion reactions (IRs) with single dose IV cetirizine 10 mg given IV push versus IV diphenhydramine 50 mg given IV push and conducted in 34 patients (21 patients ≥ 65 y.o.) receiving paclitaxel, rituximab, its biosimilar, or obinutuzumab (first cycle, retreatment after 6 months or in patients with persistent IRs).
- The primary objective was to compare the incidence of IRs after premedication. The number of patients with IRs was 2/17 (11.8%) with IV cetirizine versus 3/17 (17.6%) with IV diphenhydramine.¹ The infusion reaction rates in patients ≥ 65 was 1/9 (11.1%) for IV cetirizine versus 2/12 (16.7%) for IV diphenhydramine.^{1,6}
- The key secondary endpoints were sedation scores (range 0 to 4) due to IV antihistamines and time to readiness for discharge.¹ Sedation scores were lower at all time points studied (1 hr, 2 hr, and at discharge) in the IV cetirizine arm versus the IV diphenhydramine arm and a shorter time to discharge. This was also seen in patients ≥ 65 .
- This study demonstrated IV cetirizine is as effective as IV diphenhydramine for the prevention of IRs due to paclitaxel or an anti-CD20, with less sedation, shorter stay in the infusion center, and fewer related AEs.



- IV cetirizine has demonstrated consistent findings in three separate clinical trials versus IV diphenhydramine as outlined in (Table 1) below.^{1-3,6}

Table 1. IV Cetirizine Clinical Trial Data

	Acute Urticaria Phase 2 Study ⁶		Acute Urticaria Phase 3 Study ^{3,6}		Pre-treatment Phase 2 Study ^{1,6}	
	IV Cetirizine N = 16	IV DPH N = 17	IV Cetirizine N = 127	IV DPH N = 135	IV Cetirizine N = 17	IV DPH N = 17
Median Age (range), years	29 (20-85)	39 (19-64)	36 (18-92)	37 (18-87)	65 (36-83)	67 (45-87)
Pruritus Score (0-3) (0=no pruritis, 3=severe pruritis) IRs n (%)	Pruritis score -1.67	Pruritis score -1.60	Pruritis score -1.61	Pruritis score -1.50	IRs 2 (11.8%)	IRs 3(17.6%)
Key Secondary Endpoint: Mean Sedation Score (0=none, 3 or 4 = extreme drowsiness)	Sedation Scale 0-4		Sedation Scale 0-3		Sedation Scale 0-4	
1 hour	NA	NA	0.62	1.10	0.5	1.3
2 hours	NA	NA	0.46	0.88	0.6	0.9
Discharge	0.25	0.71	0.46	0.86	0.1	0.4
Mean time to readiness of discharge (hours)	1h 39min	2h 14min	1h 42min	2h 6min	4h 18min	4h 42min
Difference, (Minutes) All Patients	35.0		24.0		24.0	
Difference, (Minutes) ≥ 65 yo	NA		100.0*		30.0	
Treatment-Related AEs	0	4	1	9	2	4

*n = 7 in IV Cetirizine arm, n=8 in IV Diphenhydramine arm. Mean time spent in treatment center in the IV cetirizine arm was 1.35 hours and 3.01 hours in the IV Diphenhydramine arm.

Supporting References

1. Holmes JP, Dasanu CA, Peguero J, et al. A phase 2 exploratory study of intravenous cetirizine versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions in patients with breast cancer and other malignancies. Poster presentation at the 38th Annual Miami Breast Cancer Conference; 2021 Mar 4, virtual.
2. QUZYTIR (cetirizine hydrochloride injection) [package insert]. Deerfield, IL: TerSera Therapeutics LLC.; 2020.
3. Abella BS, Berger WE, Blaiss MS, et al. Intravenous cetirizine versus intravenous diphenhydramine for the treatment of acute urticaria: a phase III randomized controlled noninferiority trial. *Ann Emerg Med*. 2020 Oct;76(4):489-500.
4. Diphenhydramine hydrochloride injection [package insert]. Franklin Lakes, NJ: BD Rx Inc.; 2012.
5. 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.
6. Data on File. TerSera Therapeutics LLC.

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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