Chemotherapy-Induced Nausea and Vomiting: Developing Drugs for Prevention

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Chemotherapy-Induced Nausea and Vomiting: Developing Drugs for Prevention Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adults.[2] Specifically, this guidance addresses FDA's current recommendations on clinical trials for drugs being developed under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) and 21 CFR Parts 312 and 314 for the *prevention* of CINV and considerations for eligibility criteria, trial design features, efficacy evaluations, and clinical outcome assessments.[3]

This guidance does not address the development of drugs for the *treatment* of CINV or the prevention or treatment of nausea and vomiting unrelated to the administration of chemotherapeutic agents.[4]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law.

[1] This guidance has been prepared by the Division of Gastroenterology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of drugs for the treatment of CINV.

[4] This guidance includes recommendations for development programs for drugs for the prevention of CINV for patients receiving single-day antineoplastic therapy. FDA recommends that sponsors assess the efficacy, dosing, and safety of drugs for the prevention of CINV in patients receiving multiday antineoplastic therapy independently from those receiving single-day regimens.

FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

CINV has been identified by cancer patients as the adverse effect of treatment with the highest impact on their quality of life. An estimated 80 percent of patients undergoing chemotherapy experience CINV. CINV can cause decreased appetite, compromised nutrition, and dehydration that can progress to metabolic derangements. Inadequate control of CINV can lead to patient noncompliance or withdrawal from antineoplastic therapies, directly impacting overall prognosis.

With the known burden and potential implications of these symptoms, providing preventative treatment for CINV is the standard of care for patients undergoing chemotherapy with moderately or highly emetogenic agents. A combination of drugs from multiple therapeutic classes is frequently required to achieve optimal prevention of CINV, and recommendations for preventative treatment regimens are available from several professional organizations, including the American Society of Clinical Oncology (ASCO).[5,6]

ASCO guidelines define chemotherapy regimens (including combination regimens) associated with a 90 percent or higher incidence of nausea and vomiting in the absence of antiemetic prophylaxis as highly emetogenic chemotherapy (HEC) and regimens associated with a 30 to 90 percent incidence of vomiting as moderately emetogenic chemotherapy (MEC). FDA recommends that sponsors use these definitions of HEC and MEC when designing drug development programs.

CINV is further classified by the onset of symptoms relative to the timing of chemotherapy administration into acute phase (onset 0 through ≤24 hours) and delayed phase (onset >24 through ≤120 hours). The overall phase of CINV is defined as symptoms that are present from 0 to 120 hours following chemotherapy administration.

[5] Hesketh, PJ, MG Kris, E Basch, K Bohlke, SY Barbour, RA Clark-Snow, MA Danso, K Dennis, LL Dupuis, SB Dusetzina, C Eng, PC Feyer, K Jordan, K Noonan, D Sparacio, MR Somerfield, and GH Lyman, 2017, Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update, J Clin Oncol, 35(28):3240–3261.

[6] For additional preventative treatment guidelines, see the National Comprehensive Cancer Network, available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf; the Multinational Association of Supportive Care in Cancer Guidelines, available at https://www.mascc.org/clinical-guidelines; and the European Society for Medical Oncology, available at https://www.esmo.org/guidelines/supportive-and-palliative-care/prevention-of-chemotherapy-and-radiotherapy-induced-nausea-and-vomiting.

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors developing drugs for the prevention of CINV should consider the following when selecting clinical trial populations:

- To support an indication for the prevention of acute, delayed, or acute and delayed nausea and vomiting associated with HEC, patients should receive chemotherapy classified as HEC by the ASCO guidelines, such as cisplatin.

- Although ASCO reclassified anthracycline/cyclophosphamide (AC) chemotherapies from MEC to HEC in 2011, AC chemotherapy has been demonstrated to be less emetogenic than other agents classified as HEC (i.e., cisplatin). FDA does not consider data obtained solely from AC chemotherapy–based trials adequate to demonstrate substantial evidence of effectiveness in patients receiving other HEC regimens. Programs including patients treated with AC chemotherapy should include multiplicity-controlled analyses of the primary and secondary endpoints limited to patients receiving non-AC HEC (per ASCO guidelines) to support a demonstration of efficacy for patients receiving HEC.

- Available data show that drugs demonstrated to be effective at preventing CINV in a population receiving HEC are also effective at preventing CINV in patients receiving MEC. Therefore, FDA may consider approving an indication for the prevention of CINV in patients receiving MEC based on sufficient data to support the safe use of the drug in the MEC population, together with demonstration of effectiveness in adequate and well-controlled trials in patients receiving HEC.

- If an indication for the prevention of CINV in patients receiving MEC is being sought independently, the trial population or populations should receive chemotherapeutic agents classified as MEC by the ASCO guidelines.

- Patients with brain metastases should be included in early drug development trials to facilitate the collection of data to inform the development of eligibility criteria in later-phase trials. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol.[7]

[7] For additional recommendations, see the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Brain Metastases* (July 2020). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

B. Trial Design[8]

Sponsors developing drugs for the prevention of CINV should consider the following when designing clinical trials:

- Patients should receive standard of care background antiemetic therapy in accordance with the ASCO guidelines. These regimens should be protocol-specified, standardized, and given to all patients in both treatment groups to facilitate the interpretation of the test drug's safety and effectiveness.

- FDA recommends a randomized, double-blind, placebo-controlled trial design for sponsors that intend to demonstrate superiority of their drug added to standard of care compared with standard of care alone.

- FDA recommends a randomized, double-blind, active comparator trial design for sponsors that intend to demonstrate noninferiority or superiority to an approved therapy.[9] Such a trial should include the following arms:

  – Active Comparator: Standard of care antiemetic prophylaxis (drugs from two to four classes as recommended by ASCO)

  – Investigational Treatment: Standard of care antiemetic prophylaxis (drugs from two to four classes as recommend by ASCO) with the investigational product replacing the drug of the same class used in the comparator arm

- Permitted rescue medications and their administration schedule should be protocol-specified and standardized.

C. Efficacy Considerations

Sponsors developing drugs for the prevention of CINV should consider the following:

1. Efficacy Assessments

- To establish efficacy for the prevention of CINV, FDA recommends the following:

  – A primary efficacy endpoint of complete response, defined as no vomiting and no use of rescue antiemetic medication

[8] For additional recommendations and considerations for clinical trial populations, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[9] For additional recommendations and considerations for noninferiority clinical trial designs, see the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

- A secondary endpoint of the absence of nausea, defined as no nausea and no use of rescue antiemetic medication[10]

- Sponsors should prespecify the acute phase (0 through ≤ 24 hours), the delayed phase (>24 through ≤ 120 hours), or acute and delayed phases to define the period or periods for efficacy endpoint assessments, depending on the mechanism of action of the drug and when the primary treatment effects are anticipated.

- Sponsors may include a secondary endpoint of the assessment of efficacy in the overall phase (onset within 0 through ≤ 120 hours). FDA does not recommend sponsors select the overall phase for primary efficacy assessments, as drugs are often found to be effective for either acute or delayed onset CINV, and this information is needed to inform optimal use.

- To support the efficacy of a drug for repeat courses of chemotherapy, FDA recommends that efficacy be demonstrated during at least four chemotherapy cycles.

2. Statistical Considerations

- FDA recommends sponsors analyze the primary endpoint (i.e., a binary endpoint defined as no vomiting and no use of rescue antiemetic medication) and secondary endpoint (i.e., a binary endpoint defined as no reported nausea and no use of rescue antiemetic medication) by evaluating the difference in the proportions of responders across treatment arms.

- To gain precision in evaluating overall treatment effects, FDA recommends that statistical analyses adjust for patient characteristics at baseline that may impact efficacy outcomes, (e.g., younger age, female sex, a history of morning sickness, history of no or low use of alcohol, history of previous chemotherapy, the presence of central nervous system lesions, and history of motion sickness). Sponsors should also consider exploring subgroup analyses and potential treatment interactions based on these factors.

- Sponsors should prespecify the approach to ensure tight control of type I error rate when testing multiple endpoints (i.e., primary and secondary endpoints) that are clinically meaningful and for which labeling claims may be of interest.

- If treatment effects are anticipated in both the acute and the delayed phases, these analyses should also be appropriately controlled for multiplicity.

[10] Demonstrating significant treatment effect on the primary endpoint of complete response (no vomiting and no use of rescue antiemetic medication) in the absence of a significant treatment effect on the secondary endpoint (no nausea and no use of rescue antiemetic medication) may not be sufficient to support an indication for the prevention of the nausea component of the CINV indication.

D. Clinical Outcome Assessments

Sponsors developing drugs for the prevention of CINV should consider the following when using clinical outcome assessments (e.g., patient-reported outcome and observer-reported outcome instruments):

- FDA recommends collecting data related to the severity of the patient's nausea at its worst during the recall period (e.g., using a verbal rating scale with response options such as none, mild, moderate, and severe), assessing frequency and/or duration of nausea, and assessing impacts of nausea on the patient's daily living and functioning. The design of the instrument selected (including the specific response options in the questions included) should be informed by qualitative data from patients to demonstrate that the measurement strategy adequately captures patients' experiences with nausea.[11]

- Sponsors should use instruments with daily assessments (e.g., using a recall period of the past 24 hours), and respondents should complete the instruments at the same time each day (e.g., in the evening before bedtime). Instruments should measure the primary endpoint of complete response (i.e., no vomiting and no use of rescue medication) and the secondary endpoint of no nausea and no use of rescue antiemetic medication, using either the same or different instruments for each endpoint.

- Sponsors should seek FDA input about selecting or developing appropriate instruments and endpoints for their drug development program as early as possible and at important milestones throughout the drug development process.

[11] For additional recommendations, see the guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020). For general recommendations for patient-reported outcome assessments (as well as information relevant to other clinical outcome assessments) and the document to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).