Postoperative Nausea and Vomiting: Developing Drugs for Prevention

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Mary Chung at 301-796-0260.

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

October 2024
Clinical/Medical

Postoperative Nausea and Vomiting: Developing Drugs for Prevention

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

October 2024
Clinical/Medical

TABLE OF CONTENTS

Postoperative Nausea and Vomiting: Developing Drugs for Prevention Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to help sponsors in the clinical development of drugs[2] for the prevention of postoperative nausea and vomiting (PONV) in adults. Specifically, this guidance provides recommendations regarding the design of clinical trials for drugs for the prevention of PONV, including considerations for eligibility criteria, trial design features, efficacy evaluations, and safety assessments.[3]

This guidance does not address the development of drugs for the *treatment* of PONV. Additionally, this guidance does not address the development of drugs for the prevention of PONV in pediatric patients.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and 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

PONV is a common and distressing complication of surgery occurring within the 0- to 24-hour postoperative period in approximately 30 percent of the general surgical population and

[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* refer to drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355).

[3] In addition to consulting guidances, sponsors should contact the Division to discuss specific issues that arise during the development of drugs for the prevention of PONV.

increasing to as high as 80 percent in high-risk patients.[4] PONV can be associated with decreased appetite, compromised nutrition and hydration, and prolonged hospitalization. Additional complications of inadequately controlled PONV include esophageal tears, wound dehiscence, and decreased self-care and functional ability.[5]

Several risk factors have been associated with the development of PONV in adults. These include patient-specific risk factors (e.g., female sex, a history of PONV and/or motion sickness, nonsmoking status, and younger age), intraoperative risk factors (e.g., type of surgery [cholecystectomy, laparoscopic, bariatric, and gynecological surgeries have been associated with increased risk] and anesthesia administered [volatile anesthetic agents, such as halothane, isoflurane, desflurane, and sevoflurane; and nitrous oxide have been associated with increased risk]), and postoperative risk factors (e.g., opioid administration).[4,5,6] Volatile anesthetic agents are the primary cause of early PONV within the 0- to 2-hour postoperative period, and the risk of PONV has been found to be dependent on the dose and duration of administration of these agents.[7] Current clinical guidelines recommend that adults with at least one of the identified risk factors receive combination pharmacological PONV prophylaxis, which includes drugs from more than one pharmacological class that act on different receptor sites.[4,5]

III. DEVELOPMENT PROGRAM

A. Trial Population[8]

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

[4] Apfel, CC, E Läärä, M Koivuranta, C-A Greim, and N Roewer, 1999, A Simplified Risk Score for Predicting Postoperative Nausea and Vomiting: Conclusions From Cross-Validations Between Two Centers, Anesthesiology, 91(3):693–700.

[5] Gan, TJ, KG Belani, S Bergese, F Chung, P Diemunsch, AS Habib, Z Jin, AL Kovac, TA Meyer, RD Urman, CC Apfel, S Ayad, L Beagley, K Candiotti, M Englesakis, TL Hedrick, P Kranke, S Lee, D Lipman, HS Minkowitz, J Morton, and BK Philip, 2020, Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting, Anesth Analg, 131(2):411–448.

[6] Roberts, GW, TB Bekker, HH Carlsen, CH Moffatt, PJ Slattery, and AF McClure, 2005, Postoperative Nausea and Vomiting Are Strongly Influenced by Postoperative Opioid Use in a Dose-Related Manner, Anesth Analg, 101(5):1343–1348.

[7] Apfel, CC, P Kranke, MH Katz, C Goepfert, T Papenfuss, S Rauch, R Heineck, C-A Greim, and N Roewer, 2002, Volatile Anaesthetics May Be the Main Cause of Early but Not Delayed Postoperative Vomiting: A Randomized Controlled Trial of Factorial Design, Br J Anaesth, 88(5):659–668.

[8] For recommendations and considerations regarding enrolling and retaining a representative clinical trial population, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- Participants should be scheduled to undergo an operative procedure in which general inhalational anesthesia will be provided.

- Participants should have two or more established risk factors for the development of PONV to facilitate the identification of a treatment effect.

B. Trial Design

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

- Participants meeting the inclusion criteria recommended in section III.A typically receive combination pharmacological PONV prophylaxis, which is consistent with clinical consensus guidelines. The regimen should be protocol-specified and standardized. With the exception of the investigational product and active comparator or placebo, as applicable, the same regimen should be given to all participants.

- Trials should be randomized, double-blind, and controlled. Sponsors can consider an active-controlled superiority or noninferiority[9] trial if an investigational product is anticipated to provide greater or similar benefit, respectively, than the drug designated as the active control within a standard-of-care combination pharmacological PONV prophylaxis regimen. Sponsors can consider a placebo-controlled superiority trial, in which all participants receive the same background standard-of-care combination pharmacological PONV prophylaxis, if an investigational product is intended to provide greater benefit than the standard-of-care regimen alone.

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

C. Efficacy Considerations

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

1. Efficacy Assessments

- To establish efficacy for the prevention of PONV, sponsors should assess the following:

  – A primary efficacy endpoint of complete response should be defined as no vomiting and no use of rescue antiemetic medication in the 24 hours immediately following the completion of the operative procedure.

  – A secondary endpoint of the absence of nausea should be defined as no nausea and no use of rescue antiemetic medication in the 24 hours immediately following the

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

completion of the operative procedure.[10]

2. Statistical Considerations

- Sponsors should 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.

- Sponsors should adjust statistical analyses for baseline participant characteristics and other related factors that may impact efficacy outcomes (e.g., age, female sex, history of PONV and/or motion sickness, nonsmoking status, opioid administration) in order to gain precision when evaluating overall treatment effects. Sponsors should also consider exploring subgroup analyses and potential treatment interactions based on these factors.

- Sponsors should prespecify the approach to ensure control of the type I error rate when testing multiple endpoints (i.e., primary and secondary endpoints) for which labeling claims may be of interest. If an endpoint will be tested for both noninferiority and superiority, each test should be prespecified in the multiple testing procedure and appropriate methods should be used to control the type I error rate across both tests.

D. Safety Considerations

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

- As trials of drugs for the prevention of PONV include administration of combination pharmacological PONV prophylaxis, assessments of potential interactions between the investigational product and coadministered drugs, including allowable rescue medications, should be conducted early in development.

- Some antiemetic drugs have the potential to cause QT prolongation. The timing and frequency of electrocardiogram assessments should be based on the arrhythmogenic potential of the investigational product, as well as the arrhythmogenic potential of coadministered drugs, including allowable rescue medications. Sponsors should consider the potential for combined effects on the QT interval due to drug co-administration.

- Drug-specific considerations may alter the minimum acceptable size of the safety database, including whether the drug in question is a new molecular entity or has relevant supportive safety data from other populations, the known and anticipated adverse events of the drug and drug class, and nonclinical findings.

[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 indication.