

**FDA Briefing Document**

**Joint Meeting of Anesthetic and Analgesic Drug Products Advisory  
Committee and Drug Safety and Risk Management Advisory  
Committee**

**February 14, 2018**

## **DISCLAIMER STATEMENT**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 209-257, Hydexor (a fixed-dose combination of hydrocodone, acetaminophen, and promethazine), submitted by Charleston Laboratories, to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

# **FOOD AND DRUG ADMINISTRATION**

## **Center for Drug Evaluation and Research**

### *Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety & Risk Management Advisory Committee*

**February 14, 2018**

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## DIVISION DIRECTOR MEMO



### FDA CENTER FOR DRUG EVALUATION AND RESEARCH DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

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#### MEMORANDUM

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DATE: January 18, 2018

FROM: Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and Addiction Products  
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests  
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)  
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the February 14, 2018 AADPAC/DSaRM Meeting to Discuss  
NDA209257

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At this joint meeting of AADPAC and DSaRM, we will be discussing a new drug application from Charleston Laboratories, Inc., for an immediate-release, fixed-dose combination formulation of hydrocodone, acetaminophen, and promethazine, with the proposed tradename, Hydexor. The addition of promethazine to a hydrocodone/acetaminophen combination is intended to reduce or prevent the occurrence of opioid induced nausea and vomiting. Opioid-induced nausea and vomiting can be a major problem for some patients receiving opioids for pain, and it is the Applicant's goal to address this need. The proposed indication for Hydexor is the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The Sponsor proposes that Hydexor is to be indicated when alternative treatments for pain are inadequate. Clinical studies were conducted in patients who were prone to opioid-related nausea and vomiting. The Applicant plans to market only one strength of Hydexor; hydrocodone 7.5 mg/acetaminophen 325 mg/promethazine 12.5 mg.

The Applicant relied in part on prior findings of efficacy and safety for the components of the product by showing bioequivalence to previously approved products. In addition, the Applicant was required to comply with the “combination rule,” (21CFR 300.5) and demonstrate that each component of the combination contributes to the claimed effects of the product. Lastly, the Applicant had to show that the addition of promethazine to hydrocodone/acetaminophen resulted in superiority to placebo for the management of pain, and, was safe and effective in preventing and reducing nausea and vomiting in the study population.

An additional aspect of this application was an assessment of the abuse potential of Hydexor compared to a hydrocodone and acetaminophen combination product. Hydexor was not formulated to have any abuse-deterrent properties. The Agency requested this study to address concerns that the addition of promethazine may increase the abuse potential of the product by decreasing opioid-related nausea or vomiting or by potentiating the opioid effects of euphoria.

The FDA presentations and background documents include findings from the FDA’s review of the pharmacokinetics, efficacy and safety of Hydexor, results and interpretation of the abuse-potential study conducted by the Applicant, the epidemiologic data about the abuse of promethazine with opioids, and drug utilization trends for hydrocodone-acetaminophen combinations, promethazine-containing products, and selected immediate-release opioid analgesics.

We will ask you to discuss the Applicant’s and Agency’s findings for this application, including concerns you may have regarding the efficacy and safety of Hydexor in patients for whom it is prescribed as well as public health implications regarding the potential abuse of this product in the community. We will also ask you to discuss whether the data support the proposed indication, and whether the drug should be approved.

We request that you provide your expertise, your experience and your best insights to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this application. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

### Draft Points to Consider

1. Does the Applicant's clinical program support the safe and effective use of Hydexor for the proposed indication?
2. There are currently no immediate-release, hydrocodone-acetaminophen combination products with abuse deterrent properties that are approved and on the market. Do you have concerns that Hydexor does not have abuse-deterrent properties?
3. Are you concerned that the addition of promethazine to this product will result in abuse of Hydexor beyond the known abuse and associated harms associated with currently available hydrocodone-acetaminophen products?



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Date:** January 5, 2018

**To:** **Members of the Joint Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management (DSaRM) Advisory Committee**

**From:** **Division of Risk Management (DRISK)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)**

**Drug Name:** Hydexor (hydrocodone 7.5 mg, acetaminophen 325 mg, promethazine 12.5 mg) oral tablets

**Application Number:** NDA 209257

**Subject:** **Risk Evaluation and Mitigation Strategy (REMS)**

The Agency continues to monitor use, misuse, and abuse of prescription opioid analgesics. Of the approximately 216 million prescriptions for opioid analgesics dispensed from U.S. outpatient retail pharmacies in 2016, approximately 91% were for immediate-release (IR) formulations.<sup>1</sup> Consistent with this wide availability, recent data indicate that IR opioid analgesics continue to be associated with large numbers of intentional abuse exposure calls to poison control centers and reports of recent abuse among individuals entering treatment for substance use disorders.<sup>2</sup>

In accordance with section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), the FDA has determined that a REMS is necessary for opioid analgesics that are expected to be used in the outpatient setting to ensure the benefits of the drugs outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. On September 28, 2017, FDA notified all application holders of immediate-

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<sup>1</sup> IQVIA National Prescription Audit (NPA). Year 2016. Extracted March 2017.

<sup>2</sup> Iwanicki JL, Severtson SG, McDaniel H, et al. Abuse and Diversion of Immediate Release Opioid Analgesics as Compared to Extended Release Formulations in the United States. PLoS One. 2016;11(12):e0167499.

release (IR) opioid analgesics that are expected to be used in the outpatient setting that are not already covered by another REMS program informing them of this requirement. The letter further informed the application holders that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs for drugs with similar serious risks, FDA determined that all application holders should work together, using the existing infrastructure of the Extended-Release/Long-Acting (ER/LA) Opioid Analgesics REMS, to develop a shared system Opioid Analgesics REMS.

The Opioid Analgesic REMS is intended to reduce risks and improve safe use of opioid analgesics while continuing to provide access to these medications for patients in pain. The proposed Opioid Analgesic REMS must include the following:

**Medication Guide:** FDA has determined that opioid analgesics used in the outpatient setting poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Hydexor. FDA has determined that Hydexor is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Hydexor. FDA has also determined that Hydexor is a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all opioid analgesics, as well as product specific information that is necessary for safe and effective use of the drug.

**Elements to Assure Safe Use:** Elements to assure safe use are necessary to mitigate the serious risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse, listed in the labeling of the drug. The REMS must include elements to mitigate these risks, including at least the following:

1. The applicant must ensure that training is provided to prescribers who prescribe Hydexor and other healthcare providers involved in the treatment and monitoring of patients with pain. See draft FDA Blueprint Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To minimize the burden on the healthcare delivery system, FDA expects applicant holders to meet this requirement by providing educational grants to accredited independent continuing education (CE) providers who offer training to prescribers at no or nominal cost.
2. The applicant must provide to health care providers involved in the treatment and monitoring of patients with pain information that those health care providers can use to educate patients in the safe use, storage, and disposal of opioids.
3. The applicant must inform prescribers and other health care providers involved in the treatment and monitoring of patients with pain (e.g., pharmacists, nurses) of the existence of the REMS and the need to successfully complete the necessary training.



**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be at 6 months and 1 year and then annually from the date of the approval of this REMS.

Because Hydexor (hydrocodone, acetaminophen, promethazine) is an immediate-release opioid analgesic expected to be used in the outpatient setting, FDA has determined that this product will need a REMS to ensure that the benefits outweigh the risks and should be part of the shared system Opioid Analgesic REMS.

Attachments: Appendix A

## **Appendix A**

### **FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain (May 2017)**

(Draft Revisions to FDA Blueprint for Prescriber Education  
for Extended-Release and Long-Acting Opioids)<sup>3</sup>

## **Section 1: The Basics of Pain Management**

### **I. DEFINITIONS AND MECHANISMS OF PAIN**

Pain can be categorized according to its duration, underlying pathophysiology of the original insult, and whether a central sensitization component has developed. An understanding of these different categorizations can help direct therapeutic decisions.

Pain can be classified as follows:

1. Acute vs. chronic – Health care providers (HCPs) should be knowledgeable about the differences in the classification of pain based on how long it is expected to last.
2. Neuropathic vs. non-neuropathic – HCPs should be knowledgeable about the mechanisms underlying pain and the differences between nociceptive and neuropathic pain, and peripheral and central neuropathic pain.

### **II. ASSESSING PATIENTS IN PAIN**

HCPs should be knowledgeable about how to fully assess each patient when initiating a pain management program. When appropriate, standardized scales can be used to help document pain characteristics and guide management decisions throughout treatment.

Important elements of an initial assessment include the following:

1. Patient History –A complete history should be obtained. As part of the history of the pain condition, include prior evaluation such as diagnostic studies and types of past prior pharmacologic and nonpharmacologic treatment attempts and response. Any history of

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<sup>3</sup> This document is part of the [Extended-Release and Long-Acting \(ER/LA\) Opioid Analgesics REMS Program](#) accessed April 12, 2017

substance use, psychiatric history, family history of substance abuse and psychiatric disorders should be obtained and documented.

2. Screening tools should be used to evaluate known risk factors for development of chronic pain after an acute injury or disease.
3. Screening tools should be used to evaluate the known risk factors for opioid use disorder or abuse (e.g., structured interview tools).
4. Pain assessment scales/tools – The nature of pain should be fully documented.
5. Functional assessment scales – When pain or the associated disease interferes with physical or emotional function, disease specific or general quality of life scales should be used for documentation.
6. Physical Examination – A thorough physical exam should be conducted with any findings documented and followed that could influence analgesic choice or underlying pain condition.
7. Psychosocial Evaluation – This should be considered, particularly for patients with chronic pain.
8. Diagnostic Studies – Such studies should be considered to assist in determining cause of pain, particularly acute pain without clear precipitating event, or chronic pain not responding to conservative therapy.
9. Proper documentation – The overall treatment approach and plan should be well documented in the patient record. All patient interactions and treatment plans should be documented. Documentation can include written agreements/documentation and informed consent/patient provider agreements (PPAs).

## **Section 2: Creating the Pain Treatment Plan**

A comprehensive treatment plan should be developed and customized to the needs of the individual patient. The treatment plan should include the types of therapies planned, the goals of treatment, and an explanation of the patient and prescriber roles and responsibilities. The treatment plan should also include goals related to pain interfering with life activities such as school, work, and social activities.

### **I. COMPONENTS OF AN EFFECTIVE TREATMENT PLAN**

1. The goals of treatment – It is important to establish a set of goals early in the course of treatment, including expectations about the following:
  - The degree of improvement in pain
  - The degree of improvement in function, where relevant
2. Possible constituents of the treatment plan – The HCP should be knowledgeable about which therapies can be used to manage pain and how these should be implemented.
  - Nonpharmacologic therapies – includes psychological, physical rehabilitative, surgical approaches; and complementary therapies
  - Pharmacologic therapies – non-opioid, opioid, and adjuvant medications

3. Patient/HCP interaction – There should be a plan for patient/prescriber/health care team interaction during treatment, including expectations about the following:
  - Patient responsibilities/compliance with the plan
  - Responsibilities of the prescriber and health care team
  - Plans for reviewing functional goals
  - Use of supplemental immediate release (IR) opioids for intermittent increases in pain
  - Use of PPAs – HCPs should be knowledgeable about the role of PPAs
    - PPAs can help ensure that patients and caregivers understand the goals and the risks of treatment and how to use the medications safely.
    - PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.

## **II. NONPHARMACOLOGIC THERAPIES**

A number of nonpharmacologic therapies are available that can play an important role in managing pain, particularly musculoskeletal pain and chronic pain.

- Psychological approaches – e.g., cognitive behavioral therapy
- Physical rehabilitative approaches – e.g., physical therapy, occupational therapy
- Surgical approaches
- Complementary therapies – e.g., acupuncture, chiropractic

HCPs should be knowledgeable about the range of available therapies, when they may be helpful, and when they should be used as part of a multidisciplinary approach to pain management.

## **III. GENERAL PRINCIPLES OF PHARMACOLOGIC ANALGESIC THERAPY**

Pain can arise from a broad variety of causes. A number of analgesics are available that can be used to manage the symptoms of pain. HCPs should be knowledgeable about the range of analgesics available and the types of pain that may be responsive to those analgesics.

### **A. Non-opioid analgesics and adjuvant medications**

HCPs should be knowledgeable about the pharmacologic alternatives to opioid analgesics that can be used for pain management, including non-opioid analgesics and adjuvant medications. The following are examples of non-opioid analgesics and adjuvant medications that can be used to manage pain. (This list is not all-inclusive.)

1. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen
2. Antiepileptic drugs
3. Antidepressants
4. Local and regional anesthetics
5. Other miscellaneous adjuvant medications

When using non-opioid analgesics and adjuvant medications in pain management, HCPs should be knowledgeable about the following:

1. Mechanism of action of analgesic effect
2. Indications and uses for pain management
3. Routes of administration and formulations used in pain management
4. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
5. Contraindications
6. Adverse events
7. Drug-drug interactions – both pharmacodynamic and pharmacokinetic

## **B. Opioid analgesics**

HCPs should be knowledgeable about the risks associated with opioid analgesics as they pertain to their patients and from a public health perspective.

1. Epidemic of prescription opioid drug abuse – HCPs should be knowledgeable about the extent of the problem. HCPs should understand that most of the opioids available for misuse and abuse in the community originate from prescriptions for individual patients.
2. Paradigm shift in opioid prescribing – HCPs should be knowledgeable about existing information about safe opioid practices, current federal and state regulations, and guidelines on opioid prescribing<sup>4,5,6</sup> and the use of naloxone.

When using opioid analgesics as part of pain management, HCPs should be knowledgeable about the following:

1. General precautions
  - a. Even at prescribed doses, opioid analgesics carry the risk for misuse, abuse, addiction, overdose, and death
  - b. Importance of prescription drug monitoring programs (PDMPs)<sup>7</sup>
  - c. DSM V criteria for opioid use disorder and the concepts of abuse (taking an opioid to get high) vs. misuse (taking more than prescribed for pain or giving to someone else in pain)<sup>8</sup>
  - d. The concepts of tolerance and physiological dependence and how they differ from opioid use disorder (addiction)
  - e. Some opioid analgesics are only safe for opioid-tolerant patients
2. Mechanism of action and analgesic effect – opioid receptors and opioid action

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<sup>4</sup> [2013 Federation of State Medical Boards Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain](#) accessed on February 22, 2017.

<sup>5</sup> [Dowell D, Haegerich TM, Chou R. CD Guideline for Prescribing Opioids for Chronic Pain –United States, 2016. MMWR Recomm Rep 2016; 65 \(No.RR-1\): 1-49](#) accessed February 22, 2017.

<sup>6</sup> [SAMHSA Opioid Overdose Prevention Toolkit, updated 2016](#) accessed February 22, 2017.

<sup>7</sup> [SAMHSA Prescription Drug Monitoring Programs: A Guide for Healthcare Providers](#) accessed April 12, 2017.

<sup>8</sup> [American Psychiatric Association DSM-5-Opioid Use Disorder Diagnostic Criteria](#) accessed April 12, 2017.

- Types of opioids (synthetic phenylpiperidines, synthetic pseudo piperidines, naturally occurring alkaloids)
3. Indications and uses for pain management
    - Acute vs. chronic pain vs palliative care vs breakthrough cancer pain
  4. Routes of administration and formulations used in pain management
    - a. Formulations – immediate release (IR) vs extended release (ER) vs long-acting (LA)
    - b. Transdermal patches and important interactions with heat, magnetic resonance imaging (MRI) risk with some transdermal patches
    - c. Abuse-deterrent formulations (ADFs)
      - Definition of ADF – These drugs make abuse by certain routes more difficult, but do not prevent abuse or alter risk for addiction
      - Most common methods of opioid abuse
      - Guidance for Industry, Abuse-deterrent opioids – evaluation and labeling<sup>9</sup>
      - FDA-approved ADF products currently available
  5. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
    - a. Relative potency vs. conversion factors – HCPs should have knowledge of the concepts and limitations of the conversion charts in labeling and the concepts and limitations of equianalgesic dosing tables in literature
    - b. Variability of response
    - c. Special populations – HCPs should be knowledgeable about additional factors to consider when managing pain in the following settings.
      - Opioids during pregnancy and neonatal abstinence syndrome – HCPs should discuss the potential risks and benefits of opioids during pregnancy, including the need to anticipate and treat neonatal opioid withdrawal syndrome
      - Dosage adjustment for renal and hepatic impairment
      - Opioid use in children and adolescents
      - Opioid use in older adults
      - Sleep disorders and opioids
      - Common and uncommon psychiatric disorders, pain, and opioids
  6. Contraindications
  7. Adverse Events
    - Medication errors
    - Serious adverse drug reactions
    - Common adverse drug reactions
  8. Drug-drug interactions – both pharmacodynamic and pharmacokinetic
    - Pharmacokinetic interactions based on metabolic pathway
    - Drugs that have pharmacokinetic and not just pharmacodynamic interactions with alcohol

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<sup>9</sup> See FDA guidance for industry [Abuse-Deterrent Opioids – Evaluation and Labeling](#). accessed April 12, 2017.

- Concerns with particular drug-drug interactions
    - Benzodiazepines and other central nervous system depressants
    - Monoamine oxidase inhibitors
    - Antidiuretic hormone drugs
9. Safe use of opioids
    - a. Strategies to prevent opioid overdose/death
      - Dosing instructions
      - Safe storage
        - Risk of accidental exposure/ingestion by household contacts, especially children/teens
        - Risk of theft
      - Proper disposal of used (e.g. transdermal patches) and unused opioids
      - Encouraging availability of naloxone for all patients with opioid prescriptions
      - Seeking emergency medical treatment if an opioid overdose occurs
    - b. Pain management after an opioid overdose – HCPs should recognize that patients who have survived an opioid overdose are at much greater risk for future overdoses.
    - c. Driving and work safety

#### **IV. MANAGING PATIENTS ON OPIOID ANALGESICS**

HCPs should be knowledgeable about the appropriate use of opioids in patients with acute and chronic pain.

##### **A. Initiating treatment with opioids – acute pain**

1. Patient selection – when is an opioid necessary?
2. Dosing
  - a. As needed vs. around-the-clock
  - b. Matching expected duration of pain with quantity of analgesic prescribed
  - c. Using lower doses as long as possible, avoiding ER/LAs when pain is not expected to be present for an extended period of time and can be suitably managed with an IR
3. HCPs should prescribe and discuss the use of naloxone products as a means of avoiding death due to overdose
4. Periodic review and monitoring for patients on opioid analgesics
5. Screening tools for risk of abuse

##### **B. Initiating treatment with opioids – chronic pain**

1. Patient selection
  - a. Chronic pain vs. palliative care

- b. HCPs should know which products and which doses are indicated for use in only opioid-tolerant patients
  - c. Screening tools for known risk factors for abuse
2. Dosing
    - a. As needed vs. around-the-clock – HCPs should consider as needed dosing before initiating around-the-clock treatment.
    - b. HCPs should be knowledgeable about the warning signs and symptoms of significant respiratory depression from opioids and monitor patients closely, especially at the time of treatment initiation and dose increases.
    - c. Initial dose – HCPs should be knowledgeable about how to determine a safe initial dose and how to follow patients initiating an opioid analgesic regimen.
    - d. Titration – HCPs should know the safe interval for titration of an opioid dose taking into consideration the half-life of the product and the amount of all opioid medication used.
    - e. Safe conversion from other opioids – HCPs should be knowledgeable about the concepts and limitations of the conversion charts in labeling and the concepts and limitations of equianalgesic dosing tables in literature.
  3. Considerations in opioid selection
    - a. When to go from IR to ER/LA – HCPs should be knowledgeable about when it is appropriate to prescribe IR and ER/LA opioid analgesics.
    - b. Special precautions with methadone – HCPs should know that methadone has a longer half-life than the duration of analgesia, dosing multiple times per day for pain results in accumulation, and can prolong the QT interval.
    - c. Products restricted to opioid-tolerant patients – HCPs should be knowledgeable about the important information for each analgesic, including which opioids are indicated for use in only opioid-tolerant patients for safety reasons.
  4. HCPs should prescribe and discuss the use of naloxone products as a means of avoiding death due to overdose.
  5. When an IR should be added to an ER/LA analgesic – HCPs should be knowledgeable about when and how to supplement pain management with IR analgesics, opioids and non-opioids.

**C. Periodic review and monitoring for patients on opioid analgesics**

1. Review pain and functional goals – HCPs should evaluate patients periodically and determine if the therapy is achieving the desired goals.
2. Review adverse events – HCPs should review adverse events at each visit, with a particular focus on changes.
  - Screening for endocrine function may be recommended



3. Review refill history/reviewing PDMP – HCPs should review the patient’s refill history and refer to the state PDMP(s) available at each visit watching for evidence that the patient may have a developing problem.
4. How to determine when opioid analgesic no longer necessary/beneficial – HCPs should be knowledgeable about when the use of an opioid analgesic should be discontinued based on an integrated assessment of the goals of treatment, adverse events, and any evidence of aberrant drug use behaviors.

#### **D. Long-term management**

1. Evaluating the patient with worsening pain – Before increasing opioid dosage, HCPs should be knowledgeable about the need to reassess the underlying condition in patients with worsened pain and consider whether any signs of abuse are present.
2. Opioid rotation – When managing patients with chronic pain and long-term opioid therapy, HCPs should be knowledgeable about when it can be helpful to change the opioid, understand the safety concerns that can arise based on the following concepts, and follow the patient closely for signs and symptoms of respiratory depression and sedation until a stable dose of the new analgesic is established.
  - a. HCPs should be knowledgeable about the concept of incomplete cross-tolerance when converting patients from one opioid to another.
  - b. HCPs should be knowledgeable about the concepts and limitations of the conversion charts in labeling and the limitations of equianalgesic dosing tables in literature.
  - c. HCPs should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by the following:
    - Recognizing, documenting, and addressing aberrant drug related behavior
    - Differentiating abuse-related behavior from inadequate pain management
    - Understanding the utility and interpretation of urine drug testing (e.g., screening and confirmatory tests), and using it as indicated
    - Screening and referring for substance abuse treatment as indicated
    - Performing medication reconciliation as indicated

#### **E. When to consult with a pain specialist**

HCPs should be knowledgeable about when to appropriately refer high-risk patients to pain management specialists and when to refer patients who have not been able to achieve adequate pain management.

#### **F. Medically directed opioid tapering**

HCPs should be knowledgeable about how to safely taper opioid analgesics, including how to recognize and manage signs and symptoms of opioid withdrawal.

#### **G. Importance of patient education**

HCPs should be knowledgeable about their role in reducing the risks associated with opioids through patient education at initiation of an opioid and during long-term management of patients taking opioids.

1. HCPs should counsel the patient on how to take the opioid analgesic as prescribed.
2. HCPs should inform patients about pain management expectations and managing pain through different modalities (non-opioids, rest, physical therapy, occupational therapy, etc.) when appropriate.
3. HCPs should be aware of and use the *Patient Counseling Document* and *Medication Guide* as part of discussion with patients and caregivers when prescribing opioid analgesics.
4. HCPs should counsel the patient about the following:
  - a. Serious adverse events that can lead to death and that can occur even when product is used as recommended
  - b. Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, allergic reactions, among others
  - c. Most common side effects (e.g., constipation, nausea, headache, dizziness), and the risk of falls, working with heavy machinery, and driving
  - d. When to call the prescriber (e.g. managing adverse events, ongoing pain)
  - e. The importance of adherence to dosing regimen, how to handle missed doses, and need to contact prescriber should pain not be controlled
  - f. The importance of telling the prescriber about all of the medications they are taking and not adding other CNS depressants/other opioids/benzodiazepines without discussing these with the prescriber as the combination has the potential to cause overdose and death
  - g. Product-specific concerns, such as not to crush or chew extended-release products; transdermal patches and buccal films should not be cut, torn, or damaged before use; how to properly measure oral solution doses; and when appropriate to sprinkle the contents of a capsule
  - h. How to safely taper dose and not abruptly discontinue
  - i. Safe storage and disposal, risks of theft by family members and household visitors
  - j. Never to share any opioid analgesic with another person
  - k. How and when to use naloxone products
  - l. Seek emergency medical treatment if an opioid overdose occurs
  - m. How to report adverse events to the FDA (1-800-fda-1088 or via <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>)
5. HCPs should have training on how to begin the process of intervention should an HCP suspect abuse (how to begin the conversation and get substance abuse treatment for patients).

## **V. ADDICTION MEDICINE PRIMER**

HCPs should be knowledgeable about the basic elements of addiction medicine and be familiar with opioid use disorders as well as neurobiology and pharmacotherapy.

1. Overview of the neurobiology of opioid use disorder (addictive cycle)
2. Use of screening tools to identify patients at risk, based on known risk factors, and to identify patients developing a problem as early as possible
3. Management of opioid use disorder – HCPs should know the types of pharmacologic and nonpharmacologic treatments available and when to refer to an addiction medicine specialist.
4. Concurrent pain and opioid use disorder – HCPs should know when to refer to a pain medicine and/or addiction medicine specialist.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Drug Utilization Review**

Date: January 9, 2018

Reviewer(s): LCDR Jennie Wong, Pharm.D.  
Drug Utilization Data Analyst  
Division of Epidemiology II

Team Leader: Rajdeep Gill, Pharm.D.  
Drug Utilization Data Analysis Team Leader  
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Deputy Director: LCDR Grace Chai, Pharm.D.  
Deputy Director for Drug Utilization  
Division of Epidemiology II

Associate Director: Judy Staffa, Ph.D., R.Ph.  
Associate Director for Public Health Initiatives  
Office of Surveillance and Epidemiology

Subject: Utilization trends of hydrocodone-acetaminophen,  
promethazine-containing, and other selected immediate-release  
opioid analgesic products

Drug Name(s): Hydexor™ (hydrocodone, acetaminophen, promethazine) oral  
tablets, 7.5mg/325mg/12.5mg

Application Type/Number: NDA 209257

Applicant/sponsor: Charleston Laboratories Inc.

OSE RCM #: 2017-2291

\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\*

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## **EXECUTIVE SUMMARY**

Hydexor™ is a fixed dose combination product (hydrocodone, acetaminophen, promethazine) with a proposed indication for the short-term management of acute pain severe enough to require an opioid analgesic while preventing opioid-induced nausea and vomiting (OINV). On February 14, 2018, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held to discuss this New Drug Application (NDA) 209257. The purpose is to discuss the efficacy and safety of this product that contains an opioid analgesic and acetaminophen in combination with an anti-emetic, and no abuse-deterrent properties. To provide context and background information, this review examines U.S. outpatient retail utilization of combination hydrocodone-acetaminophen, selected opioid analgesic comparators, and promethazine-containing products from 2012 through 2016.

The utilization of combination hydrocodone-acetaminophen decreased, from 45 million patients and 125 million prescriptions dispensed in 2012, to 37 million patients and 83 million prescriptions dispensed in 2016. The top prescriber specialties for combination hydrocodone-acetaminophen were general practice/family practice/internal medicine, followed by nurse practitioners and physician assistants, and dentists. Based on office-based physician survey data for 2016, ondansetron was the most frequently reported drug for the outpatient treatment of nausea and vomiting, and combination hydrocodone-acetaminophen and promethazine-containing products were generally not prescribed together by the same prescriber during the same office-visit.

## **1 INTRODUCTION**

### **1.1 BACKGROUND**

Hydexor™ (hydrocodone, acetaminophen, promethazine immediate-release tablet) is a combination fixed dose product with no abuse-deterrent properties. The proposed indication is for the short-term management of acute pain severe enough to require an opioid analgesic, while preventing and reducing opioid-induced nausea and vomiting.

The purpose of this Advisory Committee meeting is to discuss the benefits and risks of this product. In preparation for this upcoming meeting, DAAAP has requested DEPI II to provide utilization data for combination hydrocodone-acetaminophen and promethazine-containing products to provide informational context and background information.

### **1.2 PRODUCT INFORMATION<sup>i</sup>**

Hydexor™ (hydrocodone 7.5 mg, acetaminophen 325 mg, promethazine 12.5 mg), is a combination fixed dose immediate-release tablet. The proposed indication is for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting.

### 1.3 MOLECULES INCLUDED

Table 1 provides the list of molecules included in this review:

Opioid Analgesics Molecules
<ul style="list-style-type: none"><li>• Oral Immediate-release (IR) <b>combination</b><ul style="list-style-type: none"><li>➢ Hydrocodone-Acetaminophen</li><li>➢ Oxycodone-Acetaminophen</li></ul></li><li>• Oral Immediate-release (IR) <b>single-ingredient</b><ul style="list-style-type: none"><li>➢ Hydromorphone</li><li>➢ Morphine</li><li>➢ Oxycodone</li><li>➢ Oxymorphone</li><li>➢ Tapentadol</li></ul></li></ul>
Promethazine-Containing Products
<ul style="list-style-type: none"><li>• Oral and rectal<ul style="list-style-type: none"><li>➢ Single-ingredient<ul style="list-style-type: none"><li>▪ Promethazine</li></ul></li><li>➢ Combination<ul style="list-style-type: none"><li>▪ Promethazine-Codeine-Phenylephrine</li><li>▪ Promethazine-Codeine</li><li>▪ Promethazine-Dextromethorphan</li><li>▪ Promethazine-Meperidine</li><li>▪ Promethazine-Phenylephrine</li><li>▪ Promethazine-Pseudoephedrine</li></ul></li></ul></li></ul>

## 2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. See Appendix [2] for detailed description and limitation of the databases.

### 2.1 DATA SOURCES USED

The IQVIA, National Sales Perspectives™ (NSP) database was used to determine the retail, non-retail, and mail-order channels of distribution for combination hydrocodone-acetaminophen and promethazine-containing products.

The IQVIA, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for combination hydrocodone-acetaminophen from U.S. outpatient retail pharmacies, from 2012-2016, annually.

The IQVIA, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for combination hydrocodone-acetaminophen, selected opioid analgesic comparators, and promethazine-containing products from U.S. outpatient retail pharmacies, from 2012-2016, annually. In addition, this database was also utilized to obtain nationally estimated number of prescriptions dispensed, stratified by prescriber specialties for combination hydrocodone-acetaminophen products in 2016.

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain

Panel, a U.S. office-based physician survey database was used to obtain information on the concomitant prescribing by the number of drug occurrences<sup>1</sup> associated with combination hydrocodone-acetaminophen or promethazine (single-ingredient and combination) with other drugs in 2016. Diagnoses data by number of drug use mentions<sup>2</sup> associated with the prescribing of promethazine-containing products were captured for the same time-period. Essentially drug occurrences and drug use mentions are synonymous in that they capture the number of times a drug is mentioned during patient encounters. In addition, International Classification of Diseases (ICD-10-CM) codes for nausea and vomiting were selected to capture the number of drug use mentions of drugs intended to treat nausea and vomiting in the office-based setting for the same time-period. The following ICD-10 codes were selected: R110 nausea, R111 vomiting, R112 nausea with vomiting (unspecified), O210 mild hyperemesis gravidarum, O211 hyperemesis gravidarum with metabolic disturbance, O212 late vomiting of pregnancy, O218 other vomiting complicating pregnancy, O219 vomiting of pregnancy (unspecified), and G43A cyclical vomiting.

### 3 RESULTS

#### 3.1 SETTINGS OF CARE

Sales data for 2016 indicated that 79% of combination hydrocodone-acetaminophen and 90% of promethazine-containing product sales were distributed to outpatient retail pharmacies<sup>ii</sup>. Thus, only outpatient retail pharmacy utilization patterns were examined. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

#### 3.2 UNIQUE PATIENT DATA

The nationally estimated number of patients who received a dispensed prescription for combination hydrocodone-acetaminophen decreased by approximately 19%, from 45 million patients in 2012 to 37 million patients in 2016, from U.S. outpatient retail pharmacies<sup>iii</sup> (Data not shown).

#### 3.3 OUTPATIENT DISPENSED PRESCRIPTIONS

##### 3.3.1 Opioid analgesics

**Figure 3.3.1 and Table 3.3.1 in Appendix 1** provide the nationally estimated number of dispensed prescriptions for combination hydrocodone-acetaminophen and selected opioid analgesic comparators from U.S. outpatient retail pharmacies from 2012 through 2016, annually. The total number of prescriptions dispensed for combination hydrocodone-acetaminophen decreased by nearly 34% from approximately 125 million prescriptions dispensed in 2012 to 83 million prescriptions dispensed in 2016.

Prescription volume for combination oxycodone-acetaminophen IR, hydromorphone IR, and tapentadol IR decrease steadily, while prescription volume for oxycodone IR, morphine IR, and oxymorphone IR, increase steadily in the examined time period.

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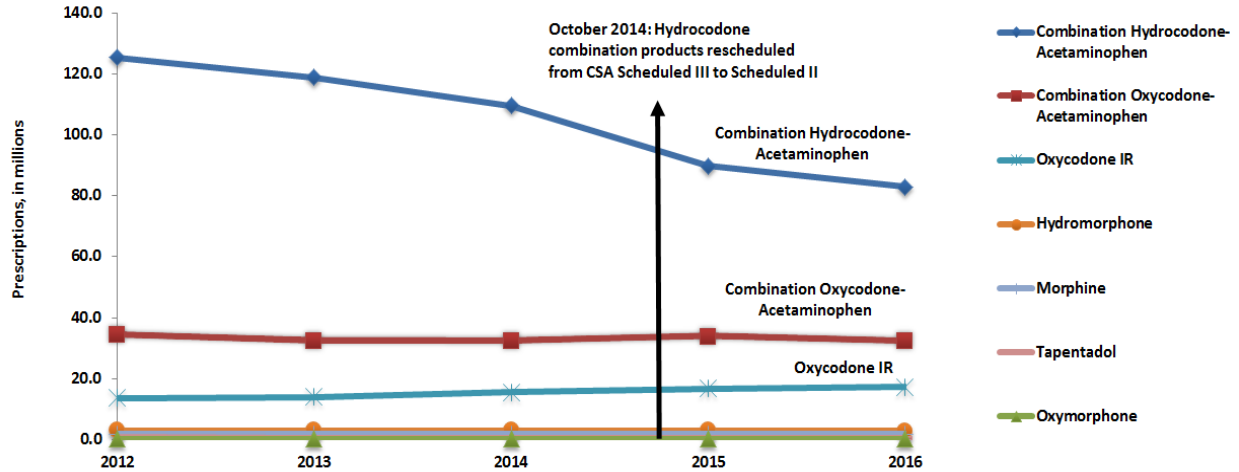
<sup>1</sup> The term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A "drug occurrence" can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

<sup>2</sup> The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.



**Figure 3.3.1**

**Nationally Estimated Number of Dispensed Prescriptions for Combination Hydrocodone-Acetaminophen and Selected Opioid Analgesic Comparators from U.S. Outpatient Retail Pharmacies**



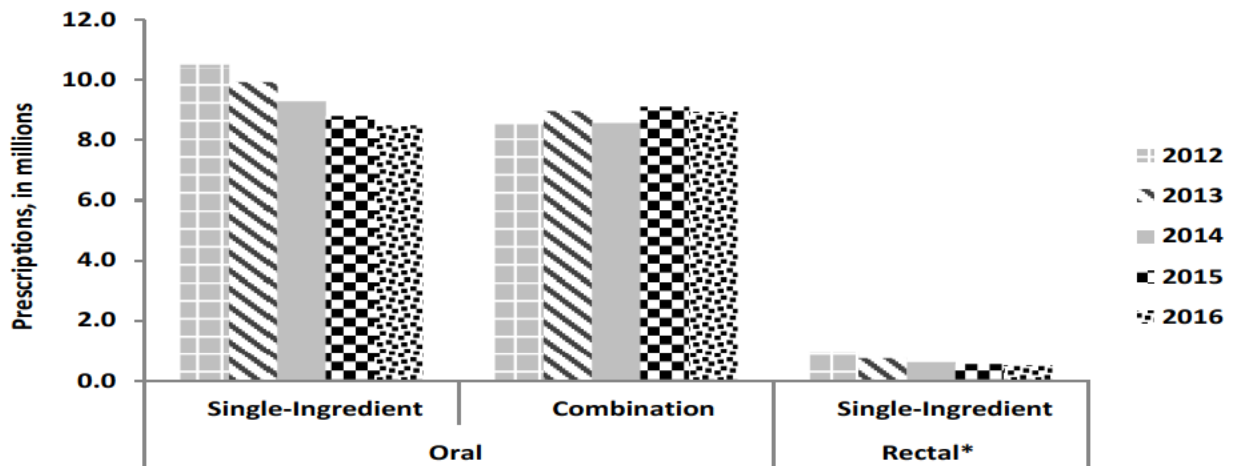
Source: IQVIA, National Prescription Audit™ (NPA). January 2012- December 2016. Data extracted November 2017.

**3.3.2 Promethazine-containing products**

**Figure 3.3.2 and Table 3.3.2 in Appendix 1** provide the nationally estimated number of dispensed prescriptions for oral and rectal promethazine-containing products, stratified by single-ingredient and combination products from U.S. outpatient retail pharmacies from 2012 through 2016, annually. The total number of dispensed prescriptions for promethazine-containing products decreased slightly by approximately 10%, from 20 million prescriptions in 2012 to 18 million prescriptions in 2016. Of the total prescriptions, the majority of the dispensed products were for an oral formulation accounting for more than 95-97%, while rectal formulation only accounted for 3-5% in the study period. Dispensed prescriptions for the oral single-ingredient promethazine products decreased by approximately 19%, from 11 million prescriptions in 2012 to 8 million prescriptions in 2016 and accounted for generally half of all dispensing of oral formulations of promethazine-containing products.

**Figure 3.3.2**

**Nationally Estimated Number of Dispensed Prescriptions for Oral and Rectal Promethazine-Containing Products, by Single-Ingredient and Combination, from U.S. Outpatient Retail Pharmacies**



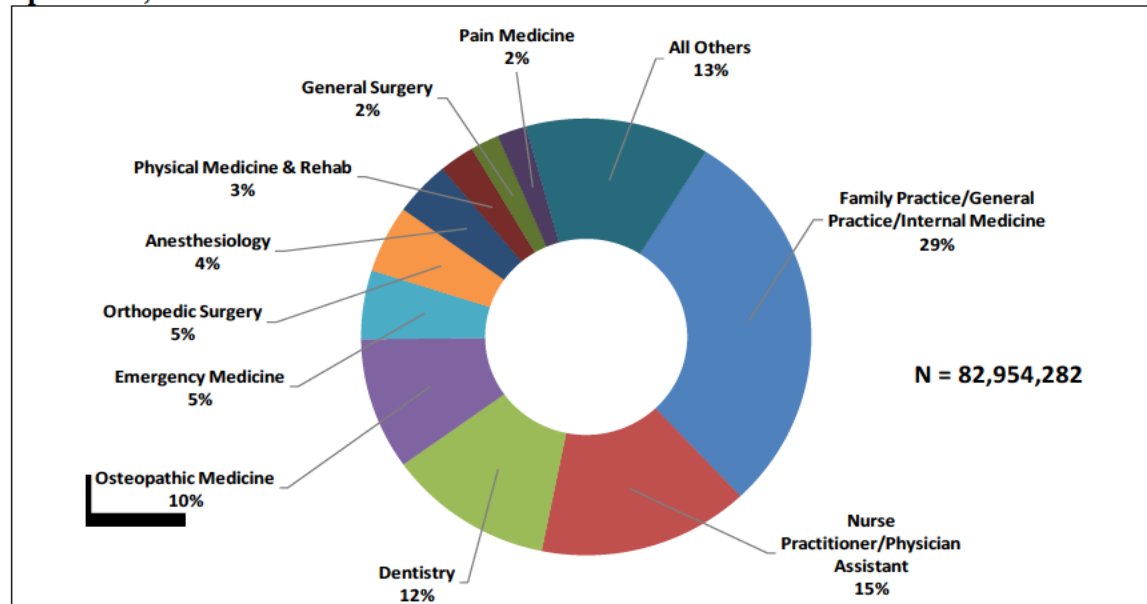
Source: IQVIA, National Prescription Audit™ (NPA). January 2012- December 2016. Data extracted November 2017.\*Note: Rectal formulation of promethazine is only available as a single-ingredient product

### 3.4 PRESCRIBER SPECIALTY DATA

Figures 3.4.1 below provides the total number of dispensed prescriptions for combination hydrocodone-acetaminophen from U.S. outpatient retail pharmacies by top prescribing specialties for 2016. General practice/family practice/internal medicine specialties were the most frequent prescribers (29% of total prescriptions), followed by nurse practitioners and physician assistants with approximately 15%, and dentistry with nearly 12% of the total combination hydrocodone-acetaminophen prescriptions dispensed.

**Figure 3.4.1**

**Nationally Estimated Number of Dispensed Prescriptions for Combination Hydrocodone-Acetaminophen from U.S. Outpatient Retail Pharmacies, Stratified by Top 10 Prescriber Specialties, 2016**



Source: IQVIA, National Prescription Audit™ (NPA). Year 2016. Data extracted November 2017.

### 3.5 U.S. OFFICE-BASED PHYSICIAN SURVEY DATA

**Table 3.5.1 below** provides the nationally estimated number of drug occurrences associated with combination hydrocodone-acetaminophen, either prescribed alone or concomitantly with another drug, as reported by U.S. office-based physician survey data for 2016. A total of 35 million drug occurrences for combination hydrocodone-acetaminophen were captured in 2016. Approximately 63% of drug occurrences associated with combination hydrocodone-acetaminophen were reported as being “used alone”. Approximately 5% of drug occurrences reported combination hydrocodone-acetaminophen to be used along with ibuprofen, followed by cephalexin (4% of drug occurrences).

There were no data captured for the concomitant drug occurrence of combination hydrocodone-acetaminophen and promethazine-containing products in 2016.

**Table 3.5.1**

**Top 10 Drug Occurrences for Combination Hydrocodone-Acetaminophen, Used Alone or with Another Molecule, as Reported from U.S. Office-Based Physician Survey Data**

	2016				
	Occurrences	Share		95% CI	
<b>Total Hydrocodone-Acetaminophen</b>	<b>34,786,000</b>	<b>100.0%</b>	<b>33,745,000</b>	—	<b>35,827,000</b>
<b>Used Alone</b>	21,890,000	62.9%	21,064,000	—	22,715,000
<b>Ibuprofen</b>	1,847,000	5.3%	1,607,000	—	2,087,000
<b>Cephalexin</b>	1,295,000	3.7%	1,094,000	—	1,496,000
<b>Cyclobenzaprine</b>	629,000	1.8%	489,000	—	768,000
<b>Gabapentin</b>	542,000	1.6%	412,000	—	672,000
<b>Morphine</b>	486,000	1.4%	363,000	—	609,000
<b>Methylprednisolone</b>	483,000	1.4%	360,000	—	605,000
<b>Naproxen</b>	471,000	1.4%	350,000	—	592,000
<b>Prednisone</b>	460,000	1.3%	340,000	—	579,000
<b>Famotidine-Ibuprofen</b>	432,000	1.2%	316,000	—	548,000
<b>All Others</b>	8,569,000	24.6%	8,052,000	—	9,085,000

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2016. Data Extracted December 2017.

Note: Syneos Health’s TreatmentAnswers system measures one level of concomitant activity. The AnswerGenerator processes a one-to-one relationship. For example, if 3 products are prescribed concomitantly and an analysis is performed on Product A, Products B and C will each receive one concomitant drug occurrence. Consequently, concomitant products will almost always add to greater than 100% of the total product occurrences.

**Table 3.5.2 in Appendix 1** provides the nationally estimated number of drug occurrences associated with promethazine (single and combination) products, either used alone or concomitantly with another drug, as reported by U.S. office-based physician survey data for 2016. For the *combination* promethazine products, approximately 41% of the drug occurrences were reported as being “used alone” and 45% of drug occurrences reported products as being used along with an antibiotic. For the *single-ingredient* promethazine products, approximately 69% of the drug occurrences were reported as being “used alone”. Approximately 13% and 4% of drug occurrences reported single-ingredient promethazine products as being used along with an antibiotic and opioid, respectively.

There were no data captured for the concomitant drug occurrence of promethazine-containing products and combination hydrocodone-acetaminophen in 2016.

### 3.6 DRUGS ASSOCIATED WITH DIAGNOSIS (ICD-10) CODES FOR NAUSEA AND VOMITING

**Table 3.6.1 below** provides the most frequently mentioned drugs associated with ICD-10 diagnosis codes for nausea and vomiting in terms of drug use mentions as reported by U.S. office-based physician surveys in 2016. A total of 15 million drug use mentions for the indications related to nausea and vomiting were captured in 2016. Of the total market, the most frequently mentioned drug was ondansetron, accounting for approximately 58% of the drug use mentions. Ondansetron was followed by single-ingredient promethazine and prochlorperazine at approximately 20% and 6% of drug use mentions, respectively. No data were captured for *combination* promethazine products related to nausea and vomiting in 2016.

**Table 3.6.1**

**Top 10 Drugs Associated with ICD-10 Diagnosis Codes for Nausea and Vomiting, Reported from U.S. Office-Based Physician Survey Data, 2016**

	2016				
	Uses	Share		95% CI	
<b>Total Market</b>	<b>14,516,000</b>	<b>100.0%</b>	<b>13,845,000</b>	—	<b>15,187,000</b>
<b>Ondansetron</b>	8,422,000	58.0%	7,911,000	—	8,933,000
<b>Promethazine Single-Ingredient</b>	2,881,000	19.9%	2,582,000	—	3,180,000
<b>Prochlorperazine</b>	935,000	6.4%	764,000	—	1,105,000
<b>Doxylamine/Pyridoxine</b>	480,000	3.3%	358,000	—	602,000
<b>Metoclopramide</b>	233,000	1.6%	148,000	—	318,000
<b>Granisetron</b>	153,000	1.1%	84,000	—	222,000
<b>Diphenhydramine</b>	127,000	0.9%	64,000	—	189,000
<b>Prenatal vitamins</b>	113,000	0.8%	54,000	—	172,000
<b>Oral electrolytes</b>	108,000	0.7%	50,000	—	166,000
<b>Dexamethasone</b>	105,000	0.7%	48,000	—	162,000
<b>All Others</b>	960,000	6.6%	788,000	—	1,133,000

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2016. Data Extracted December 2017.

### 3.7 DIAGNOSIS (ICD-10 CODES) ASSOCIATED WITH THE USE FOR PROMETHAZINE PRODUCTS

Using office-based physician survey data, the most common diagnoses associated with the use of promethazine for 2016, stratified by single-ingredient versus combination products, were reported. A total of 7 million mentions with diagnoses associated with the use of promethazine-containing products were captured. Among the single-ingredient promethazine products, the majority reported “Nausea and Vomiting” as the diagnosis associated with use (65% of drug use mentions). Among combination promethazine products, the majority reported “Cough” and “Bronchitis” as the diagnoses associated with the use of combination products (approximately 25% drug use mentions, respectively)<sup>iv</sup> (Data not shown).

## 4 DISCUSSION

The focus of this drug utilization analysis is to provide an analysis of utilization patterns in support of the upcoming advisory committee meeting to discuss a new drug application for a fixed dose combination product containing hydrocodone, acetaminophen, and promethazine with no abuse-deterrent properties.

Utilization decreased in both the patient and prescription data for combination hydrocodone-acetaminophen over the examined time. The total number of patients decreased by approximately 19%, from 45 million patients in 2012 to 37 million patients in 2016. Similarly, the total number of prescriptions dispensed decreased by nearly 34% from 125 million prescriptions in 2012 to 83 million prescriptions in 2016. The decline in utilization may partly be attributed to the rescheduling of hydrocodone-combination products that occurred in October 2014<sup>4</sup>; however, this review did not assess the factors impacting utilization patterns. Dispensed prescriptions for the oral single-ingredient promethazine products also decreased by approximately 19%, from 11 million prescriptions in 2012 to 8 million prescriptions in 2016.

US office-based physician survey data was used to characterize the concomitant prescribing of combination hydrocodone-acetaminophen or promethazine-containing products with other drugs. Our analysis indicates that hydrocodone- acetaminophen AND promethazine-containing products were generally not prescribed by the same prescriber during the same office-visit. The term "drug occurrences" refers to the number of times a product has been reported on a survey during an office-based patient visit and may not result in a dispensed prescription; rather it represents the prescriber's intention. The data presented based on surveys are likely an underestimation of the total concurrent use of these drugs as data on prescriptions written by a different prescriber or during a different visit by the same prescriber may not be reported. In addition, all utilization estimates may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed. Despite these limitations, these data do represent prescriber intent where the prescriber is aware of or intentionally prescribes the use of two or more products together. The office-based survey data also show that prescribers most frequently reported ondansetron for the treatment of nausea and vomiting in the outpatient setting.

Findings from this review should be interpreted in the context of other known limitations of the databases used. We focused our analysis on the primary setting of care for these drugs, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, inpatient, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.

## **5 CONCLUSIONS**

Drug utilization analyses show that despite the decrease in the utilization of combination hydrocodone-acetaminophen from 2012 through 2016, substantial utilization remains with approximately 83 million prescriptions dispensed in 2016. Analysis of data from office-based physician surveys suggest that combination hydrocodone-acetaminophen and promethazine-containing products were generally not prescribed together by the same prescriber during the same office-visit.

## 6 APPENDICES

### 6.1 APPENDIX 1: TABLES AND FIGURES

Table 3.3.1

**Nationally Estimated Number of Dispensed Prescriptions for Combination Hydrocodone-Acetaminophen and Selected Opioid Analgesics from U.S. Outpatient Retail Pharmacies**

	2012		2013		2014		2015		2016	
	Rx	%	Rx	%	Rx	%	Rx	%	Rx	%
<b>Total Prescriptions</b>	<b>178,879,991</b>	<b>100.0%</b>	<b>170,770,920</b>	<b>100.0%</b>	<b>162,847,263</b>	<b>100.0%</b>	<b>145,812,952</b>	<b>100.0%</b>	<b>137,678,485</b>	<b>100.0%</b>
Hydrocodone-Acetaminophen IR	125,424,574	70.1%	118,901,119	69.6%	109,591,521	67.3%	89,811,458	61.6%	82,954,282	60.3%
Oxycodone-Acetaminophen IR	34,182,548	19.1%	32,352,014	18.9%	32,277,674	19.8%	33,702,684	23.1%	32,123,248	23.3%
Oxycodone IR	13,565,218	7.6%	13,972,391	8.2%	15,445,943	9.5%	16,800,731	11.5%	17,322,451	12.6%
Hydromorphone IR	2,971,802	1.7%	2,942,455	1.7%	2,949,105	1.8%	2,942,662	2.0%	2,736,136	2.0%
Morphine IR	1,798,141	1.0%	1,826,126	1.1%	1,858,680	1.1%	1,858,568	1.3%	1,849,029	1.3%
Tapentadol IR	776,153	0.4%	592,050	0.3%	513,783	0.3%	485,771	0.3%	484,933	0.4%
Oxymorphone IR	161,555	0.1%	184,765	0.1%	210,557	0.1%	211,078	0.1%	208,406	0.2%

Source: IQVIA, National Prescription Audit™ (NPA). January 2012- December 2016. Data extracted November 2017.

Figure 3.3.2

**Nationally Estimated Number of Dispensed Prescriptions for Oral and Rectal Promethazine-Containing products, Stratified by Single-Ingredient and Combination, from U.S. Outpatient Retail Pharmacies**

	2012		2013		2014		2015		2016	
	Rx	%	Rx	%	Rx	%	Rx	%	Rx	%
<b>Total Promethazine</b>	<b>19,934,011</b>	<b>100.0%</b>	<b>19,620,855</b>	<b>100.0%</b>	<b>18,469,564</b>	<b>100.0%</b>	<b>18,427,241</b>	<b>100.0%</b>	<b>17,925,286</b>	<b>100.0%</b>
<b>Oral</b>	<b>19,011,236</b>	<b>95.4%</b>	<b>18,875,411</b>	<b>96.2%</b>	<b>17,846,433</b>	<b>96.6%</b>	<b>17,879,559</b>	<b>97.0%</b>	<b>17,416,446</b>	<b>97.2%</b>
Single Ingredient	10,502,387	55.2%	9,915,602	52.5%	9,285,397	52.0%	8,781,723	49.1%	8,485,106	48.7%
Combination	8,508,849	44.8%	8,959,809	47.5%	8,561,036	48.0%	9,097,836	50.9%	8,931,340	51.3%
<b>Rectal</b>	<b>922,775</b>	<b>4.6%</b>	<b>745,444</b>	<b>3.8%</b>	<b>623,131</b>	<b>3.4%</b>	<b>547,682</b>	<b>3.0%</b>	<b>508,840</b>	<b>2.8%</b>
Single Ingredient	922,775	100.0%	745,444	100.0%	623,131	100.0%	547,682	100.0%	508,840	100%

Source: IQVIA, National Prescription Audit™ (NPA). January 2012- December 2016. Data extracted December 2017.

Table 3.5.2

**Top 10 Drug Occurrences for Promethazine (Single and Combination) Products, Used Alone or with Another Molecule, as Reported from U.S. Office-Based Physician Survey Data in 2016**

	2016			
	Occurrences	Share	95% CI	
<b>Total Promethazine-Containing Products</b>	<b>5,015,000</b>	<b>100.0%</b>	<b>4,620,000</b>	<b>– 5,410,000</b>
<b>Combination Promethazine</b>	<b>2,897,000</b>	<b>57.8%</b>	<b>2,597,000</b>	<b>– 3,198,000</b>
<b>Used Alone</b>	1,185,000	40.9%	993,000	– 1,377,000
<b>Azithromycin</b>	576,000	19.9%	442,000	– 710,000
<b>Amoxicillin</b>	293,000	10.1%	197,000	– 388,000
<b>Doxycycline</b>	222,000	7.7%	139,000	– 305,000
<b>Clarithromycin</b>	174,000	6.0%	100,000	– 247,000
<b>Acetaminophen</b>	148,000	5.1%	80,000	– 216,000
<b>Ibuprofen</b>	78,000	2.7%	28,000	– 127,000
<b>Albuterol</b>	75,000	2.6%	26,000	– 123,000
<b>Amoxicillin-Clavulanate</b>	60,000	2.1%	16,000	– 103,000
<b>Levofloxacin</b>	49,000	1.7%	10,000	– 88,000
<b>All Others</b>	356,000	12.3%	251,000	– 461,000
<b>Single-Ingredient Promethazine</b>	<b>2,117,000</b>	<b>42.2%</b>	<b>1,861,000</b>	<b>– 2,374,000</b>
<b>Used Alone</b>	1,461,000	69.0%	1,247,000	– 1,674,000
<b>Atropine-Diphenoxylate</b>	127,000	6.0%	64,000	– 190,000
<b>Cephalexin</b>	108,000	5.1%	50,000	– 165,000
<b>Promethazine*</b>	97,000	4.6%	42,000	– 151,000
<b>Acetaminophen-Oxycodone</b>	72,000	3.4%	25,000	– 120,000
<b>Ondansetron</b>	71,000	3.4%	24,000	– 118,000
<b>Azithromycin</b>	60,000	2.8%	17,000	– 103,000
<b>Amoxicillin</b>	54,000	2.6%	13,000	– 95,000
<b>Ciprofloxacin</b>	46,000	2.2%	8,000	– 84,000
<b>Atovaquone-Proguanil</b>	46,000	2.2%	8,000	– 84,000
<b>All Others</b>	200,000	9.4%	121,000	– 279,000

\*Injectable promethazine

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2016. Data Extracted December 2017.

Note: Syneos Health’s TreatmentAnswers system measures one level of concomitant activity. The AnswerGenerator processes a one-to-one relationship. For example, if 3 products are prescribed concomitantly and an analysis is performed on Product A, Products B and C will each receive one concomitant drug occurrence. Consequently, concomitant products will almost always add to greater than 100% of the total product occurrences.

## **6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS**

### **IQVIA, National Sales Perspectives™: Retail and Non-Retail**

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IQVIA National Prescription Audit™**

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

### **IQVIA, Total Patient Tracker™ (TPT)**

TPT is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from United States retail pharmacies. Clients get access to all markets and can manipulate the period under study from 1 month to 1 year. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses the prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients, and multiple prescriptions fills, producing quick and reliable unique patient counts. Prescription coverage is 90%, has a sample of 50,400 pharmacies, and captures about 3.7 billion transactions annually. TPT is projected to the known universe.

### **Syneos Health Research & Insights, LLC., TreatmentAnswers™**

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialist physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected mentions or occurrences may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 (mentions or occurrences) do not represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level.



## 7 REFERENCES

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<sup>i</sup> DARRTS NDA 209257, Form 3674; User Fee/Coversheet; New/NDA, Supporting Document 1/eCTD0001, dated 3/31/2016

<sup>ii</sup> IQVIA, National Sales Perspectives™ (NSP). Year 2016. Data extracted December 2017.

<sup>iii</sup> IQVIA, Total Patient Tracker (TPT). Years 2012-2016. Data extracted December 2017.

<sup>iv</sup> Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2016. Data Extracted January 2018.

<sup>v</sup> Jones, C, Lurie, P, Throckmorton, D. Effect of US Drug Enforcement Administration's Rescheduling of Hydrocodone Combination Analgesic Products on Opioid Analgesic Prescribing. Journal of American Medical Association (JAMA) Internal Medicine. March 2016; 176(3):399-402. Accessed on 2/22/2016 at <http://archinte.jamanetwork.com/>



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

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**MEMORANDUM**

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DATE: January 10, 2018

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TO: Chair, Members and Invited Guests  
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)  
Drug Safety and Risk Management Advisory Committee (DSaRM)

## 1 Background

Hydexor is a fixed-dose combination drug product containing hydrocodone bitartrate, acetaminophen, and promethazine hydrochloride with a proposed indication of the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV). Charleston Laboratories, Inc. (the “Applicant” or the “Sponsor”) submitted a 505(b)(2) NDA for Hydexor relying on the Agency’s previous findings of safety and efficacy for Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg), Ultracet (tramadol hydrochloride 37.5 mg/acetaminophen 325 mg), and Phenergan (promethazine hydrochloride 12.5 mg) to support the pharmacodynamic and pharmacological properties of hydrocodone, acetaminophen, and promethazine, respectively. fixed-dose combination products that contain hydrocodone (HC) and acetaminophen have been marketed widely in the United States for decades. HC is also available in oral extended-release (ER) single-entity formulations.

Hydexor is formulated with promethazine, a phenothiazine with antiemetic properties, to address OINV in patients that require analgesia from an HC/acetaminophen product. Hydexor is provided in one strength and consists of an immediate-release bi-layered tablet with one layer containing 12.5 mg of promethazine and a second layer, containing 7.5 mg of HC and 325 mg of acetaminophen, intended to release after the promethazine. Similar to all other currently available HC/acetaminophen products, Hydexor has not been formulated with properties intended to deter abuse. Throughout these documents, Hydexor is also referred to as CL-108.

For such a fixed-dose combination product, the “combination rule” (21 CFR 300.50) requires that “...each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.” To meet this requirement, the Sponsor could have conducted full-factorial design studies to demonstrate that each of the three active ingredients made a contribution to the overall product. However, the tablets were developed to be bioequivalent (BE) for both HC and acetaminophen to an approved HC/acetaminophen product, Norco. Therefore, factorial-design studies were only needed to support the addition of promethazine.

As a result, the primary goals of the development program for Hydexor were to: 1) demonstrate BE of Hydexor to Norco for both HC and acetaminophen, 2) demonstrate the efficacy of Hydexor over Norco for prevention of OINV, and 3) characterize the safety profile of Hydexor for the stated indication.

## 2 Clinical Pharmacology

The pharmacokinetic profile (PK) of Hydexor has been obtained in three Phase 1 clinical studies (CLCT-004, CLCT-012, and CLCT-013). The hydrocodone (HC), acetaminophen, and

promethazine (PMZ) exposures from Hydexor were compared to the respective components to create a scientific bridge for the 505(b)(2) application, that is, HC, acetaminophen or PMZ to reference products, Vicoprofen (N020716; HC bitartrate 7.5 mg / ibuprofen 200 mg), Ultracet (N021123; tramadol hydrochloride (HCl) 37.5 mg / acetaminophen 325 mg), and Phenergan (N007935; PMZ HCl 12.5 mg), respectively, and, to NORCO, the comparator used in the Phase 3 trials.

After single-dose Hydexor administration, the C<sub>max</sub> and AUC values for all three components were found to be equivalent under fasted and fed states based on the 80 to 125% bioequivalence criteria, compared to reference products. Similar T<sub>max</sub> values for all three components were observed under fasted and fed states, compared to the reference products.

After single-dose Hydexor administration in the fasted condition, C<sub>max</sub> and AUC values for HC and acetaminophen were found to be equivalent based on the 80 to 125% bioequivalence criteria, compared to NORCO. Median T<sub>max</sub> values for HC and acetaminophen were similar, compared to NORCO. A graphical comparison of HC T<sub>max</sub> frequency distribution histogram indicated that Hydexor had a wider T<sub>max</sub> range, compared to NORCO.

After single-dose Hydexor administration in the fed condition, C<sub>max</sub> and AUC values for HC and acetaminophen AUC values were found to be equivalent based on the 80 to 125% bioequivalence criteria, compared to NORCO; however, acetaminophen C<sub>max</sub> from Hydexor was not bioequivalent to NORCO, as the lower 90% CI bound was not within the 80% limit (79.69%). Based on a discussion with the clinical team, although acetaminophen C<sub>max</sub> was not contained within the lower bound of 90% CI, this may not be clinically significant. A graphical comparison of acetaminophen T<sub>max</sub> frequency distribution histogram indicated that Hydexor had a wider T<sub>max</sub> range, compared to NORCO.

Details of the studies are provided below. Table 1 presents a comparison of the exposures of hydrocodone, acetaminophen, and promethazine following treatment with Hydexor, the reference products in CLCT-004, and NORCO under fasted conditions and Table 2 under fed conditions.

Table 1 Comparison of Mean (SD) PK Parameters for Hydrocodone, Acetaminophen, and Promethazine for CL-108 and Reference Products Administered under **Fasted** Conditions (CLCT-004 and CLCT-012)

Parameter	CLCT-004		CLCT-012	
	CL-108 (n=19)	Reference products <sup>a</sup> (n=20)	CL-108 (n=32)	NORCO (n=31)
Hydrocodone				
t <sub>max</sub> (h) <sup>b</sup>	1.50 (0.50-3.00)	1.00 (0.50-6.00)	1.50 (0.50-4.00)	1.00 (0.50-2.00)
C <sub>max</sub> (ng/mL)	20.0 (5.48)	18.4 (5.62)	19.3 (5.60)	17.2 (5.01)
AUC <sub>∞</sub> (ng•h/mL)	150.2 (57.30)	134.3 (48.20)	120.8 (27.21)	106.5 (28.90)

Table 1, continued				
Acetaminophen				
t <sub>max</sub> (h) <sup>b</sup>	0.75 (0.50-1.50)	0.50 (0.25-2.00)	0.75 (0.50-3.50)	0.75 (0.50-1.00)
C <sub>max</sub> (µg/mL)	4.71 (1.49)	5.02 (1.66)	4.15 (1.65)	4.34 (1.30)
AUC <sub>∞</sub> (µg•h/mL)	19.69 (5.785)	19.16 (5.33)	14.56 (4.689)	14.67 (4.953)
Promethazine				
t <sub>max</sub> (h) <sup>b</sup>	4.00 (2.50-6.00)	5.00 (2.00-8.00)	4.00 (1.00-8.00)	NA
C <sub>max</sub> (ng/mL)	4.79 (3.75)	4.35 (2.94)	4.17 (52.76)	NA
AUC <sub>∞</sub> (ng•h/mL)	96.92 (119.5)	88.53 (100.3)	53.57 (42.10)	NA

a 505(b)(2) linkage reference products - Treatment C: Hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg tablet + Ultracet tablet (tramadol HCl 37.5 mg / acetaminophen 325 mg) + promethazine HCl 12.5 mg tablet (all 3 tablets taken together) under fasted conditions.

b Median (range)

Source: clct-004-body.pdf Table 11.4.3.6;

**Table 2 Comparison of Mean (SD) Pharmacokinetic Parameters for Hydrocodone, Acetaminophen, and Promethazine for CL-108 and Reference Products Administered under Fed Conditions (CLCT-004 and CLCT-013)**

Parameter	CLCT-004		CLCT-013	
	CL-108 (n=20)	Reference product <sup>a</sup> (n=19)	CL-108 (n=30)	NORCO (n=32)
Hydrocodone				
t <sub>max</sub> (h) <sup>b</sup>	3.00 (1.00-8.00)	3.00 (0.75-6.00)	2.75 (1.50-6.00)	2.00 (0.50-3.50)
C <sub>max</sub> (ng/mL)	17.9 (5.80)	17.5 (3.63)	17.7 (4.09)	18.0 (4.54)
AUC <sub>∞</sub> (ng•h/mL)	155.8 (58.75)	152.4 (56.83)	127.9 (28.67)	120.4 (26.01)
acetaminophen				
t <sub>max</sub> (h) <sup>b</sup>	2.75 (0.75-6.00)	2.00 (0.75-6.00)	2.00 (1.00-6.00)	1.50 (0.50-3.50)
C <sub>max</sub> (µg/mL)	3.27 (1.00)	3.03 (0.919)	3.17 (0.927)	3.60 (1.17)
AUC <sub>∞</sub> (µg•h/mL)	18.56 (4.875)	18.53 (4.988)	16.13 (3.848)	16.06 (3.459)
Promethazine				
t <sub>max</sub> (h) <sup>b</sup>	6.00 (2.50-12.00)	6.00 (1.00-24.00)	6.00 (2.50-8.00)	NA
C <sub>max</sub> (ng/mL)	3.66 (2.16)	4.08 (1.95)	3.42 (2.27)	NA
AUC <sub>∞</sub> (ng•h/mL)	60.72 (29.74)	84.13 (76.72) <sup>c</sup>	60.78 (45.58)	NA

a 505(b)(2) linkage reference products - Treatment D: Hydrocodone bitartrate 7.5 mg / ibuprofen 200 mg tablet + Ultracet tablet (tramadol HCl 37.5 mg / acetaminophen 325 mg) + promethazine HCl 12.5 mg tablet (all 3 tablets taken together) under fed conditions

b Median (range); c n=18 for AUC<sub>∞</sub>

Source: clct-004-body.pdf Table 11.4.3.6;

The mean plasma half-life of HC, acetaminophen, and PMZ were estimated to be 4.9, 4.6 and 17.5 hours, respectively. PK parameters of HC, acetaminophen, and PMZ were comparable between Hydexor and the listed drug products.

505(b)(2) Scientific Bridge

Under fasted conditions, single-dose Hydexor provided an equivalent Cmax and AUC exposure compared to the reference products [see Table 1; Listed products: Vicoprofen (N020716; HC bitartrate 7.5 mg / ibuprofen 200 mg), Ultracet (N021123; tramadol hydrochloride (HCl) 37.5 mg / acetaminophen 325 mg), and Phenergan (N007935; PMZ HCl 12.5 mg)]. The 90% CIs for Cmax and AUCinf for HC, acetaminophen and PMZ were all within the accepted 80-125% limits of bioequivalence (Table 3). After single-dose Hydexor administration in fasted condition, all active ingredients had similar Tmax compared to the listed products. The Tmax frequency distribution indicated that Hydexor and listed products showed similar Tmax distribution.

Table 3 Statistical Analysis of Systemic Exposure Parameters of Hydrocodone, Acetaminophen, and, Promethazine for Hydexor versus Reference Products under **Fasted** Condition

Parameter	Geometric mean		Ratio	90% Confidence interval	
	Hydexor	Reference product*		Lower	Upper
Hydrocodone					
Cmax	19.14	17.64	108.54	97.30	121.09
AUCinf	139.96	126.65	110.51	105.85	115.37
Acetaminophen					
Cmax	4.49	4.79	93.63	83.08	105.52
AUCinf	18.85	18.39	102.47	98.40	106.71
Promethazine					
Cmax	3.68	3.58	102.72	90.34	116.80
AUCinf	60.75	61.18	99.29	91.60	107.63

\*Reference products: Vicoprofen (N020716; HC bitartrate 7.5 mg / ibuprofen 200 mg), Ultracet (N021123; tramadol hydrochloride (HCl) 37.5 mg / acetaminophen 325 mg), and Phenergan (N007935; PMZ HCl 12.5 mg)]

Under fed conditions, single-dose Hydexor provided an equivalent Cmax and AUC exposure compared to the reference products [see Table 2; Listed products: Vicoprofen (N020716; HC bitartrate 7.5 mg / ibuprofen 200 mg), Ultracet (N021123; tramadol hydrochloride (HCl) 37.5 mg / acetaminophen 325 mg), and Phenergan (N007935; PMZ HCl 12.5 mg)]. The 90% CIs for Cmax and AUCinf for HC, acetaminophen and PMZ were all within the accepted 80-125% limits of bioequivalence (Table 4). After single-dose Hydexor administration in fed condition, all active ingredients had similar Tmax compared to the listed products. The Tmax frequency distribution indicated that Hydexor and the listed products showed similar Tmax distribution.

Table 4 Statistical Analysis of Systemic Exposure Parameters of Hydrocodone, Acetaminophen, and, Promethazine for Hydexor versus Reference Products under **Fed** Condition

Parameter	Geometric mean		Ratio (%)	90% Confidence interval	
	Hydexor	Reference product*		Lower	Upper
Hydrocodone					
Cmax	17.0949	17.0793	100.09	89.72	111.66
AUCinf	145.2129	143.1030	101.47	97.20	105.94
Acetaminophen					
Cmax	3.1074	2.9065	106.91	94.86	120.49
AUCinf	17.8828	17.9172	99.81	95.84	103.94
Promethazine					
Cmax	3.3607	3.6460	92.17	80.89	105.03
AUCinf	65.9317	72.1815	91.34	83.95	99.39

\*Reference products: Vicoprofen (N020716; HC bitartrate 7.5 mg / ibuprofen 200 mg), Ultracet (N021123; tramadol hydrochloride (HCl) 37.5 mg / acetaminophen 325 mg), and Phenergan (N007935; PMZ HCl 12.5 mg]

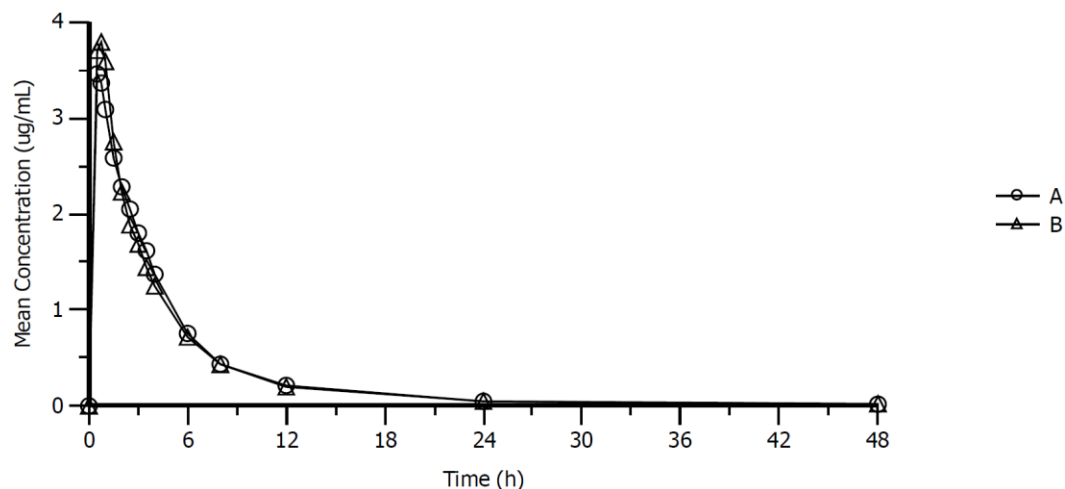
### Relative bioavailability to NORCO

Figures 1 and 2 represent concentration-time profiles for hydrocodone and acetaminophen, respectively, under fasting condition.

Figure 1 Mean Hydrocodone Concentration-Time Profiles CL-108 (Treatment A) and NORCO (Treatment B) Under Fasted Conditions

Figure 2 Mean Acetaminophen Concentration-Time Profiles CL-108 (Treatment A) and NORCO (Treatment B) Under Fasted Conditions

Analyte=Acetaminophen



Source data: clct-012-body; p.43/356

Under fasted conditions, single-dose Hydexor provided an equivalent HC C<sub>max</sub> and AUC exposures compared to NORCO. The geometric mean ratios for hydrocodone C<sub>max</sub> and AUC<sub>inf</sub> were 110.85 and 114.31%, respectively. The 90% confidence intervals were within the 80.00% to 125.00% limits for C<sub>max</sub> and AUCs (Table 5). Hydrocodone T<sub>max</sub> statistical analysis between Hydexor and NORCO indicated that there was a difference in the median (range) T<sub>max</sub> [1.50 h (0.50 - 4.00 h) and 1.00 h (0.50 - 2.00 h), respectively]. A graphical comparison of HC T<sub>max</sub> frequency distribution histogram indicated that Hydexor had a wider T<sub>max</sub> range, which may have attributed to the difference in analysis. The T<sub>max</sub> difference (median difference of 0.5 h) is minimal and may not be clinically significant.

Under fasted conditions, single-dose Hydexor provided an equivalent acetaminophen C<sub>max</sub> and AUC exposures compared to NORCO. The geometric mean ratios for acetaminophen C<sub>max</sub> and AUC<sub>inf</sub> were 91.53 and 99.74%, respectively (Table 5). The 90% confidence intervals were within the 80.00% to 125.00% limits for C<sub>max</sub> and AUCs. Acetaminophen T<sub>max</sub> statistical analysis between Hydexor and NORCO indicated that similar median (range) T<sub>max</sub> values were observed [0.75 h (0.50 - 3.50 h) and 0.75 h (0.50 - 1.00 h), respectively]. A graphical comparison of acetaminophen T<sub>max</sub> frequency distribution histogram indicated that Hydexor had a wider T<sub>max</sub> range.



Table 5 Statistical Analysis of Hydrocodone for Hydexor and NORCO Administered Under **Fasted** Conditions

Parameters	Geometric mean		Ratio (%)	90% Confidence interval	
	Hydexor	NORCO		Lower	Upper
Hydrocodone					
Cmax	18.52	16.70	110.85	102.42	119.97
AUCinf	117.97	103.20	114.31	109.62	119.21
Acetaminophen					
Cmax	3.82	4.18	91.53	81.15	103.23
AUCinf	14.08	14.12	99.74	96.12	103.49

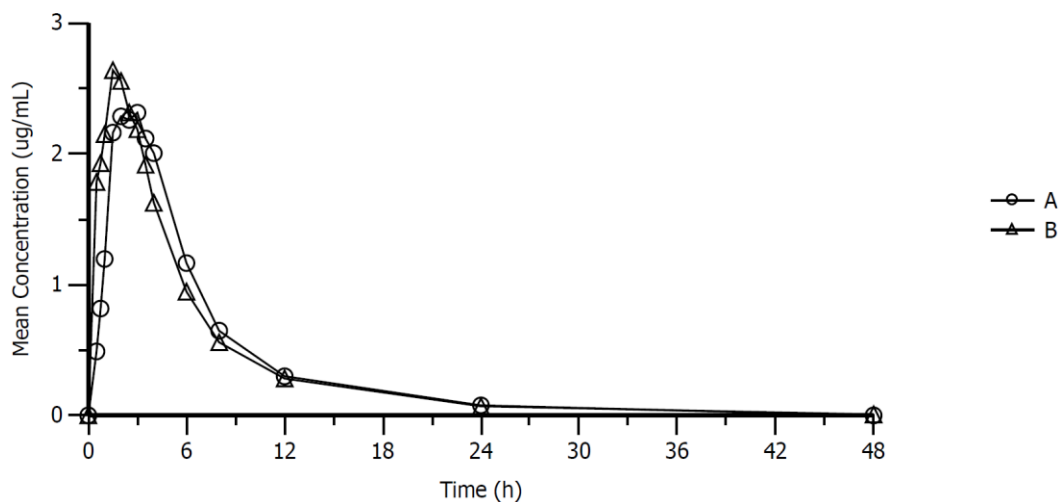
Figures 3 and 4 represent concentration-time profiles for hydrocodone and acetaminophen, respectively, under fed condition.

Figure 3 Mean Hydrocodone Concentration-Time Profiles, CL-108 (Treatment A) and NORCO (Treatment B) Under Fed Conditions

Source data: clct-013-body; p.41/332

Figure 4 Mean Acetaminophen Concentration-Time Profiles CL-108 (Treatment A) and NORCO (Treatment B) Under Fed Conditions

Analyte=Acetaminophen



Source data: clct-013-body; p.43/332

Under fed conditions, single-dose Hydexor provided an equivalent HC C<sub>max</sub> and AUC exposure compared to NORCO. The geometric mean ratios for hydrocodone C<sub>max</sub> and AUC<sub>inf</sub> were 98.97 and 105.10%, respectively. The 90% confidence intervals were within the 80.00% to 125.00% limits for C<sub>max</sub> and AUCs (Table 6). Hydrocodone T<sub>max</sub> statistical analysis between Hydexor and NORCO indicated that there was a difference in the median (range) T<sub>max</sub> [2.75 h (1.50 - 6.00 h) and 2.00 h (0.50 - 3.50 h), respectively]. A graphical comparison of HC T<sub>max</sub> frequency distribution histogram indicated that HC T<sub>max</sub> from Hydexor occurred slightly later (median difference of 0.75 h) than that of NORCO. The T<sub>max</sub> difference is minimal and may not be clinically significant.

Under fed conditions, single-dose Hydexor provided an equivalent acetaminophen AUC exposure compared to NORCO. The geometric mean ratio for acetaminophen AUC<sub>inf</sub> was 98.89% (90% CI: 96.11 - 101.75%). However, acetaminophen C<sub>max</sub> from Hydexor was not bioequivalent to NORCO, as the 90% CIs were not within the 80.00% to 125.00% limits (point estimate: 88.54%; 90% CI: 79.69 - 98.36%) (Table 6). Based on a discussion with the clinical team, although acetaminophen C<sub>max</sub> was not contained within the lower bound of 90% CI, this small difference is likely not to be clinically significant. Acetaminophen T<sub>max</sub> statistical analysis between Hydexor and NORCO indicated that there was a difference in the median (range) T<sub>max</sub> [2.0 h (1.0 - 6.0 h) and 1.50 h (0.50 - 3.50 h), respectively]. A graphical comparison of acetaminophen T<sub>max</sub> frequency distribution indicated that acetaminophen T<sub>max</sub> from Hydexor occurred slightly later (median difference of 0.5 h) than that of NORCO. The T<sub>max</sub> difference is minimal and may not be clinically significant.

Table 27 Statistical Analysis of Hydrocodone for Hydexor and NORCO Administered Under Fed Conditions

Parameters	Geometric Mean		Ratio (%)	90% Confidence interval	
	Hydexor	NORCO		Lower	Upper
Hydrocodone					
Cmax	17.25	17.43	98.97	90.79	107.89
AUCinf	123.89	117.87	105.10	101.97	108.34
Acetaminophen					
Cmax	3.03	3.42	88.54	79.69	98.36
AUCinf	15.71	15.88	98.89	96.11	101.75

### Food Effect

No food effect was observed on Cmax and AUC for HC and PMZ (bioequivalence was established between fasted and fed comparison). For acetaminophen, no food effect was observed for AUC; however, acetaminophen Cmax was lower, with a point estimate approximately 31% less in fed state compared to fasted state (90% CI: 61.44-78.03).

Table 3 Hydexor food effect information - Cmax and AUC point-estimate changes

	HC	acetaminophen	PMZ
Cmax	10.7% decreased	30.8% decreased	8.63% decreased
AUC	3.8% increased	5.11% decreased	8.53% increased

### Implications of delayed Tmax in the fed state

When Tmax values were compared after single-dose Hydexor administration, PMZ had similar Tmax distribution across the fasted and fed states. However, for HC and acetaminophen, there were differences observed. The Tmax frequency distribution indicated that food prolonged Tmax on average 1.5 to 2 hours compared to fasted state. The Applicant stated in efficacy trials, CLCT-002 and CLCT-003, both Hydexor and NORCO were administered without regard to food. The preliminary findings from the efficacy trials indicated that Hydexor was efficacious for pain and opioid-induced nausea and vomiting, regardless of fed or fasted conditions. Therefore, it appears unlikely that administration with food affected the clinical responses observed in these studies across treatments.

From a single-dose dedicated fed pharmacokinetic study, which compared Hydexor and NORCO, the HC and acetaminophen exposures were similar. There was a slight Tmax increase for both HC and acetaminophen (median difference of 0.5 to 0.75 h) for Hydexor. Although

there is a slight difference, this minimal difference would be considered negligible and may not be clinically significant. NORCO may be used regardless of food; thus, it is reasonable to administer Hydexor without regard to food.

### **3 Clinical Efficacy**

The Applicant submitted results from two primary efficacy studies (CLCT-002 and CLCT-003) to provide evidence of efficacy for Hydexor in the proposed patient population. These studies are discussed separately below.

#### **Study CLCT-002**

##### Study Design and Endpoints

This was a randomized, double-blind, placebo-controlled, parallel-group, partial-factorial design study in adult patients with moderate-to-severe pain following dental surgery and who were anticipated to experience OINV. It was a multi-center study with 466 patients randomized at a total of seven centers in the United States.

The primary objectives of the study were to:

- Demonstrate the efficacy of Hydexor compared to placebo for the management of pain following surgical removal of impacted third molar teeth, and
- Demonstrate the efficacy of Hydexor compared to Norco for the reduction of OINV

The study used a partial-factorial design, with patients randomized to the three-drug combination (HC, acetaminophen, and promethazine; Hydexor), the two-drug combination (HC and acetaminophen; Norco), or placebo, because the HC/acetaminophen combination is not considered a novel combination as bioequivalence for HC and acetaminophen between Hydexor and Norco was established. Patients were randomized in a 4:4:1 ratio to Hydexor, Norco, or placebo. The randomization was stratified based on the patient's nausea-prone classification, either possibly nausea-prone or likely nausea-prone.

Study CLCT-002 was conducted in 2013 and was completed prior to a full discussion and agreement with the Division about acceptable outcome measures. The study was stopped after positive results were obtained on the planned interim analysis. The results were discussed with the Division, at which point the Sponsor was told that the preferred outcome measure for the OINV outcome was a combination of absence of vomiting and lack of rescue antiemetic use. The Division of Gastroenterology and Inborn Errors Products (DGIEP) relies upon this dual outcome to define efficacy of antiemetics with use of rescue antiemetics as a surrogate for significant nausea. Because the current study did not incorporate this outcome, the Division requested that the Sponsor provide a post-hoc analysis of OINV in Study CLCT-002 using this preferred outcome measure and incorporate this outcome measure into the planned second Phase 3 study, Study CLCT-003.

Patients were eligible for the study if they were 18 years and older and reported moderate-to-severe pain on the Pain Intensity Categorical Scale (PI-CAT) following extraction of at least two impacted third molar teeth. On the PI-CAT, patients are instructed to rate their pain intensity on a scale from 0 to 3, where 0=no pain, 1=minor pain, 2=moderate pain, and 3=severe pain. Patients who reported at least moderate pain on the PI-CAT, confirmed by a score of at least 50 mm on a 100 mm visual analog pain scale, within the first four hours following surgery were eligible for randomization.

In order to be able to demonstrate an effect of the promethazine, the study population was enriched for patients more likely to experience OINV, the protocol required that patients meet at least one of two criteria. Patients were required to be at least “Possibly Nausea-Prone” based on the NPQ or experience nausea or vomiting following an HC challenge during the screening period. For the HC challenge, all patients were given a single hydrocodone tablet and asked to report any nausea or vomiting during the two hours following administration. Additionally, investigators were permitted to enroll up to 10% of patients who did not meet the predefined nausea-prone criteria but were thought to be nausea-prone based on clinical judgment.

The NPQ asks patients whether they have experienced nausea when performing certain activities. The questions are divided into three categories as follows:

Category A consisted of the following questions:

- Reports being “allergic” to an opioid-containing drug and the symptoms reported are determined to be nausea or vomiting.
- Has taken an opioid-containing drug and became nauseated or vomited.
- Has taken an unknown medication after an operation or surgical procedure and became nauseated or vomited.
- Reports being “allergic” to cough medicine and the symptoms reported are determined to be nausea or vomiting.
- Has taken a cough medicine (naming the opioid in it or not) and became nauseated or vomited.

Category B consisted of the following questions:

- Easily becomes nauseated at the sight of blood.
- Easily becomes nauseated at a bad smell (such as vomit).
- Easily becomes nauseated when riding in a car (requires an open window).
- Easily becomes nauseated when riding backwards in a train.
- Easily becomes nauseated when on a roller coaster.
- Easily becomes nauseated when spun around.
- Easily becomes nauseated when bending over.
- Easily becomes nauseated when just thinking about it.
- Easily becomes nauseated with headaches.

Category C contained the following question, which patients answered using an 11-point numerical rating scale, where 0 indicated not likely and 10 was most likely:

- Think of situations where you tend to get sick to your stomach, nauseous or vomit -- such as taking a strong pain-killer or a cough medicine with codeine, gagging, riding a roller coaster, spinning around, turning around suddenly, riding in a car, sitting backwards on a train, riding in a boat, seeing blood, smelling a bad smell. In general: Do you consider yourself prone (likely) to get nauseous?"

The Sponsor classified patients as "Likely Nausea-Prone" if they responded affirmatively to at least one of the Category A questions or experienced nausea or vomiting during the HC challenge. Patients were categorized as "Possibly Nausea-Prone" if they responded affirmatively to at least three of the category B questions or reported a score of four or more for category C.

Patients that were classified as possibly or likely nausea-prone or those that were thought to be nausea-prone based on investigator discretion were eligible to proceed to the next phase of the study and were scheduled for the dental procedure.

After surgery and the first dose of the study medication, subjects remained in the clinic for six hours and were then discharged to home. In CLCT-002, patients were administered one dose at randomization, followed by one dose as needed (prn) every 4-6 hours for up to five days. (This is in contrast to the later study, CLCT-003, where patients were administered one dose at randomization, followed by one dose every 4-6 hours on a fixed schedule for the first 48 hours, then prn for Days 3-5.) Supplemental medications for pain (ibuprofen) or nausea/vomiting (antiemetic of choice) were permitted at any time. Five days after surgery, subjects returned to clinic for end-of-study assessments.

For analgesia, the primary outcome measure was the Pain Intensity Categorical Scale (PI-CAT). On the PI-CAT, patients are instructed to rate their pain intensity on a scale from 0 to 3, where 0=no pain, 1=minor pain, 2=moderate pain, and 3=severe pain. PI-CAT scores were collected at baseline, every 30 minutes until hour six, and then every hour while awake until 24 hours. The primary endpoint for each subject was the time-weighted sum of pain intensity differences over 24 hours (SPID24). The primary analysis was a comparison of the SPID24 scores between the Hydexor and placebo groups.

For OINV, the primary outcome measure was a responder analysis with responder status derived from three criteria: a nausea score, presence of vomiting recorded on a vomiting scale, and requirement for antiemetic medication. Nausea was assessed with the Nausea Intensity Scale (NIS), an 11-point numerical rating scale. On the NIS, the patient was to report the worst nausea they experienced in the past hour from 0 to 10, where a score of 0=no nausea and 10=severe nausea. Vomiting was recorded using the Vomiting Frequency Scale (VFS) where a patient reported how many incidents of vomiting they had in the last hour. For the VFS, a score of 0=no vomiting, 1=one incident in the last hour, 2=two incidents in the last hour, and 3=three or more incidents in the last hour.

For OINV, patients were considered responders if they met the following criteria during the first 24 hours of the study:

- Did not report any vomiting
- Did not report any scores of four or more on the NIS
- Did not require the use of antiemetic medication

The post hoc analysis for reduction in OINV requested by the Division was also a responder analysis, but was based on only the following two components:

- Did not report any vomiting
- Did not require the use of antiemetic medication

Four key secondary outcomes were included in the protocol and the statistical analysis plan:

- Summed intensity of nausea (on NIS) over initial 24 hours.
- Summed intensity of nausea (on NIS) over initial 6 hours.
- Frequency of vomiting (on VFS) over initial 24 hours.
- Summed intensity of nausea on the Stomach Scale (StomS) over 6 hours. The StomS is an 11-point Likert Scale where patients were asked to rate how their stomach was at its worst over the past hour, with a score of 0=normal stomach and 10=vomited.

### Statistical Methodology

There were two primary endpoints for this study. Since the Applicant was required to show a statistically significant difference in both endpoints, no correction for multiple comparisons was required. The key secondary endpoints were only to be tested if both primary endpoints were found to be significant. The type I error rate for the key secondary endpoints was controlled using a Hochberg Step-Up procedure.

Analysis of the analgesia primary efficacy endpoint: This endpoint was analyzed using a linear model with treatment arm, site ID, and baseline pain as covariates. Missing data prior to first use of rescue or early withdrawal was replaced with the last observed pain score. Observed or missing pain scores after rescue use were replaced with the baseline pain score. Missing data after early withdrawal were replaced with the result recorded at the early withdrawal visit, if available.

Analysis of the opioid induced nausea/vomiting primary efficacy endpoint: This endpoint was analyzed using a logistic regression model with treatment, investigator, and baseline nausea-prone status as main effects. The 2-component version recommended by DGIEP was analyzed using the same approach.

Analysis of the key secondary endpoints: The frequency of vomiting endpoint was analyzed using a Poisson regression model, with treatment, investigator, and baseline nausea-prone status as main effects. The other three key secondary endpoints were analyzed using a general linear model with treatment, investigator, and nausea-prone status as main effects.”

The FDA Statistical Reviewer additionally performed a number exploratory analyses to investigate the observed nausea/vomiting event rates in patients with different response patterns on the screening NPQ.

### Patient Demographics and Patient Disposition

A total of 466 patients were randomized in the trial. The mean age was about 22 years, as would be expected for this dental surgical procedure. The majority of patients (72%) were female and the majority of patients were white (80%). The demographic and other background characteristics were comparable between the two treatment groups.

### **Patient Disposition, Study CLCT-002**

<b>Parameter/Category</b>	<b>CL-108 (N=211)</b>	<b>Norco (N=205)</b>	<b>Placebo (N=50)</b>	<b>Total (N=466)</b>
<b>Number of Patients</b>				
Screened				755
Randomized	211	205	50	466
Completed Study [n (%)]	209 (99.1%)	203(99.0%)	46 (92.0%)	458 (98.3%)
Discontinued Study [n (%)]	2 (0.9%)	2 (1.0%)	4 (8.0%)	8 (1.7%)
<b>Primary Reason for Discontinuation [n (%)]</b>				
Withdrawal of Consent	0	0	1 (2.0%)	1 (0.2%)
Adverse Event	0	0	1 (2.0%)	1 (0.2%)
Lost to Follow-Up	0	1 (0.5%)	0	1 (0.2%)
Lack of Efficacy	2 (0.9%)	0	2 (4.0%)	4 (0.9%)
Other	1 (0.5%)	0	0	1 (0.2%)

Source: FDA Statistical Review

The results of the nausea-prone assessments are shown in the tables below. The majority (82%) of the patients who completed the nausea-prone assessments met the Sponsor's nausea-prone criteria. Enrollment based on investigator discretion indicates that a patient did not meet the nausea-prone criteria but the investigator determined that they were still at risk for developing OINV. The Applicant only provided the responses to the individual nausea-prone questionnaire items for the randomized patients and only reported the percentage of the screened population who were found to be nausea-prone. However, the Applicant reported that one of the sites for CLCT-002 and all of the sites for CLCT-003 included questions about nausea and vomiting in the telephone pre-screening that were not described in the protocol. It appears that these questions were used to exclude patients who were not likely to be prone to nausea and vomiting from the initial screening. Therefore, the results observed for the screening NPQ cannot be considered representative of the prevalence of nausea-prone patients in the general population.



### Results of the Nausea-Prone Assessment

Nausea-Prone Screening Result	Number of Patients
Nausea-Prone	565 (82%)
Not Nausea-Prone	124 (18%)
Total	689

Source: FDA Statistical Reviewer

The table below shows the results of the nausea-prone assessments for the randomized patients. The majority (79%) of patients either reported nausea or vomiting following a previous opioid exposure or experienced nausea or vomiting following the hydrocodone challenge. The protocol allowed investigators to enroll approximately 10% of total study enrollment based on their clinical evaluation. These patients are categorized as “Investigator Discretion” in the table below.

### Results of the Nausea-Prone Assessments – Randomized Population Study CLCT-002

Category	N (%)
Likely Nausea-Prone	367 (79%)
Possibly Nausea-Prone	78 (17%)
Investigator Discretion	21 (5%)
Total	466

Source: FDA Statistical Reviewer

### Results

*Analgesia Endpoint:* Patients in the Hydexor (CL-108) treatment arm were found to have statistically significantly higher reductions in pain intensity over the first 24 hours than patients in the placebo arm. Hydexor was not formally compared to the active comparator Norco, as the addition of promethazine was not expected to improve the analgesic effects.

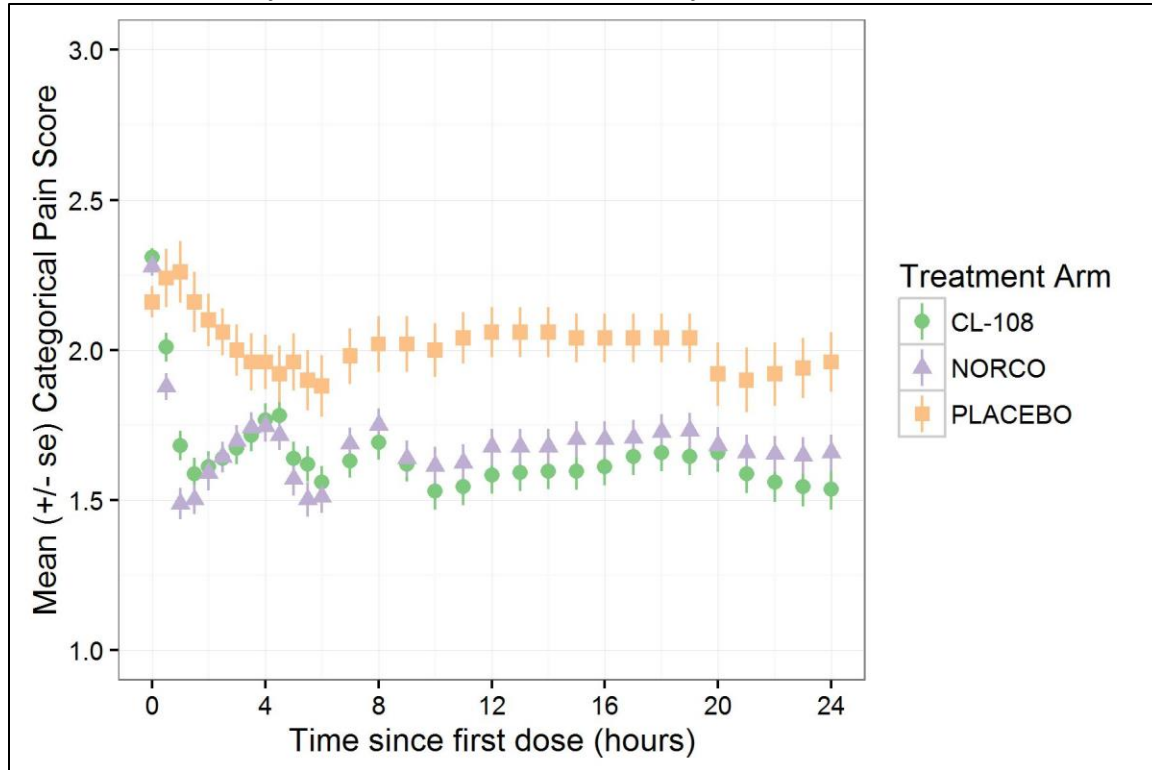
### Primary Analysis Results, Study CLCT-002, Sponsor

Endpoint	Estimate P-Value	CL-108 (N=211)	Norco (N=205)	Placebo (N=50)
<b>Analgesia Endpoint:</b>				
<b>SPID<sub>24</sub></b>				
N		211	205	50
Mean (SD)		16.2 (17.1)	14.6 (16.3)	3.5 (10.5)
Median		11.5	8.1	0.0
Min, Max		(-19, 68)	(-3, 68)	(-13, 45)
<b>CL-108 vs Placebo</b>				
LS-Means Difference	11.2			
(95% CI)	(6.7,15.7)			
P-Value	<0.001			

Source: FDA Statistical Review

The figure below shows a graph of the mean pain intensities over time for each treatment group. There is a clear separation between patients in the placebo arm and both the CL-108 and Norco treatment arms.

**Mean Pain Intensity over the First 24 Hours, Study CLCT-002**



Source: FDA Statistical Review

The following table shows the use of rescue medication. Patients in the Norco and CL-108 treatment arms used less rescue medication than patients in the placebo treatment arm. The use of rescue medication was not included as one of the key secondary endpoints and was not statistically tested.

**Rescue Use by Treatment Arm, Study CLCT-002**

<b>Rescue Medication Use</b>	<b>CL-108 (N=211)</b>	<b>Norco (N=205)</b>	<b>Placebo (N=50)</b>
Number (%)	93 (44%)	109 (53%)	43 (86%)
Mean Dose (mg) among patients requiring rescue	712	752	976

Source: FDA Statistical Review

The FDA statistical reviewer performed several sensitivity analyses exploring different imputation methods for missing data as well as the role of rescue medication use on the

outcome. There was very little missing data for the first ten hours after the first dose of study drug, but there was a considerable amount of missing data for the ten subsequent hours, corresponding to nighttime/sleep for most patients. The results of the sensitivity analyses were consistent with the Sponsor’s primary analysis above.

*OINV Endpoint:* The results for both the protocol-specified primary analysis and the post hoc analysis requested by the Division are shown in the table below. The comparisons are between the Hydexor and Norco treatment arms of the study. In both analyses, there was a statistically significant reduction in the percentage of patients who experienced nausea or vomiting. Because dosing with study drug was as needed during the study, it is important to note for purposes of the OINV outcome that use of study drug was comparable across treatment groups for the first day. On average, the Hydexor group averaged 3.5 capsules on the first day and the Norco group averaged 3.6 capsules on the first day. (The placebo group also averaged 3.3 capsules, but this is less relevant for the OINV analyses below.)

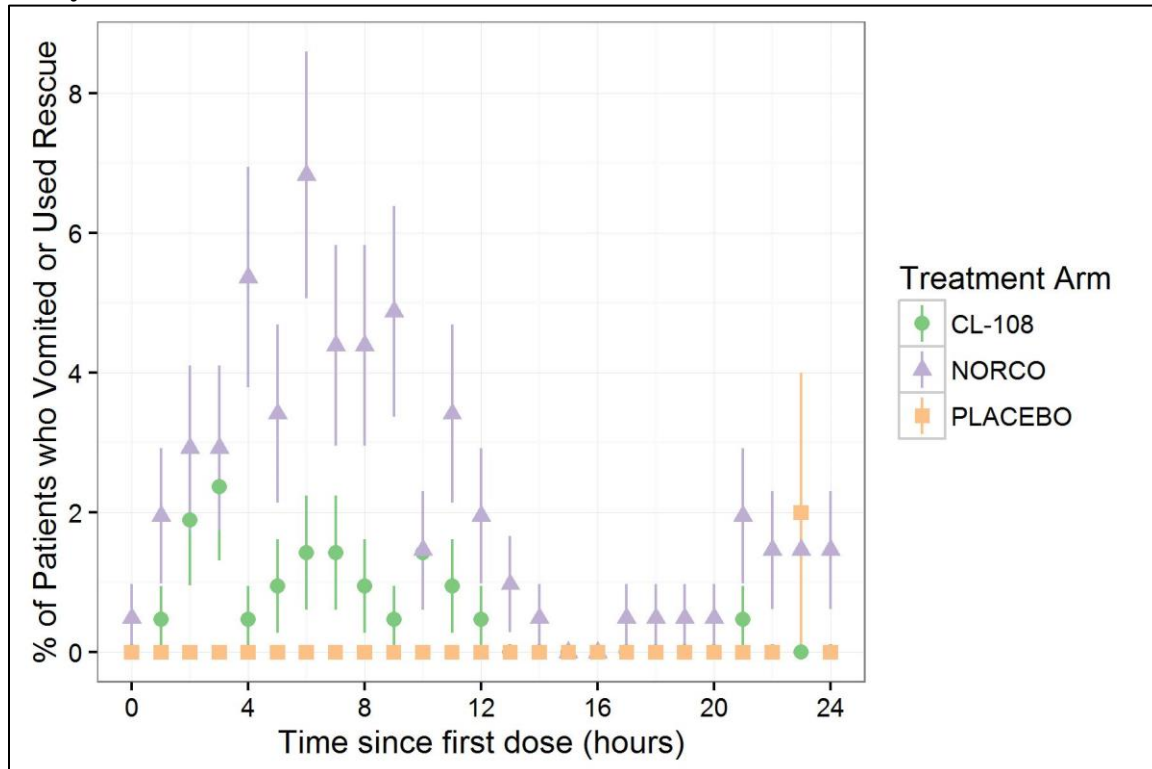
**Table 1: Assessment of the OINV Study Endpoint, Study CLCT-002**

<b>Endpoint</b>	<b>CL-108 (N=211)</b>	<b>Norco (N=205)</b>	<b>Placebo (N=50)</b>	<b>Relative Risk Reduction</b>	<b>Odds Ratio (95% CI)</b>	<b>P-Value</b>
Two Component OINV Failures (Post-Hoc)	24 (11%)	65 (32%)	2 (4%)	64%	0.26 (0.15, 0.44)	<0.001
Three Component OINV Failures (Primary)	76 (36%)	119 (58%)	9 (18%)	38%	0.37 (0.24, 0.56)	<0.001

Source: FDA Statistical Review

The between-group differences for the occurrence of vomiting or anti-emetic rescue use are demonstrated in the figure below.

**Percentage of Patients Vomiting or Using Anti-Emetic Rescue over the Previous Hour, Study CLCT-002**



Source: FDA Statistical Review

The results for all four key secondary endpoints were found to be statistically significant as shown in the table below.

**Key Secondary Endpoints, Study CLCT-002**

Endpoint	P-Value
Summed intensity of nausea (on NIS) over initial 24 hours.	< 0.001
Summed intensity of nausea (on NIS) over initial 6 hours.	0.013
Frequency of vomiting (on VFS) over initial 24 hours.	0.002
Summed intensity of nausea (on StomS) over 6 hours.	0.026

Source: FDA Statistical Review

The table below shows the results of the two-component OINV assessment broken down by nausea-prone category and treatment group. In the active treatment groups, patients that were classified as likely nausea-prone (history of OINV) failed the two-component OINV criteria at slightly higher rates than patients who were classified as being possibly nausea-prone.

### Percentage of Two-Component OINV Failures, Study CLCT-002

<b>Nausea-Prone Category</b>	<b>CL-108 (N=211)</b>	<b>Norco (N=205)</b>	<b>Placebo (N=50)</b>
Likely Nausea-Prone	21/165 (13%)	55/165 (33%)	1/37 (3%)
Possibly Nausea-Prone	3/38 (8%)	8/28 (29%)	1/12 (8%)
Investigator Discretion	0/8 (0%)	2/12 (17%)	0/1 (0%)

Source: FDA Statistical Review

Regardless of the nausea-prone classification at screening, the magnitude of reduction in OINV events for CL-108 compared to Norco appears to be similar (Likely Nausea-Prone: 20%, Possibly Nausea-Prone: 21%, Investigator Discretion: 17%) with Norco-treated patients consistently showing a greater tendency to OINV than Hydexor-treated patients.

### Study CLCT-003

#### Study Design and Endpoints

This was a randomized, double-blind, placebo-controlled, parallel-group, partial-factorial design study in adult patients with moderate-to-severe pain following bunionectomy and who were anticipated to experience OINV. It was a multi-center study with 552 patients randomized at four centers in the United States.

The primary objectives of the study were to:

- Demonstrate the efficacy of Hydexor compared to placebo for the management of pain following bunionectomy, and
- Demonstrate the efficacy of Hydexor compared to Norco for the reduction of OINV

The study used a partial-factorial design study, with patients randomized to the three-drug combination (HC, acetaminophen, and promethazine; Hydexor), the two-drug combination (HC and acetaminophen; Norco), or placebo, because the HC/acetaminophen combination is not considered a novel combination as bioequivalence for HC and acetaminophen between Hydexor and Norco was established. Patients were randomized in a 5:5:1 ratio to Hydexor, Norco, or placebo.

Following the surgical procedure, a nerve block was to be maintained until approximately 3 am on the morning after surgery. Following the removal of the nerve block, patients were observed until they reported moderate-to-severe pain on the PI-CAT, confirmed by a pain score of four or more on an 11-point numerical rating scale (PI-NRS), or 9 hours passed.

Patients were eligible for the study if they were 18 years and older and reported moderate-to-severe pain on the Pain Intensity Categorical Scale (PI-CAT) following discontinuation of the nerve block. On the PI-CAT, patients are instructed to rate their pain intensity on a scale from 0 to 3, where 0=no pain, 1=minor pain, 2=moderate pain, and 3=severe pain.

This study was also designed with a patient population enriched for patients more likely to experience OINV. This study used the same nausea-prone questionnaire that was employed in Study CLCT-002 but did not use the hydrocodone challenge. To be eligible, patients were required to be at least “Possibly Nausea-Prone” based on the NPQ alone during the screening period. Patients that were possibly or likely nausea-prone were eligible to proceed to the next phase of the study and were scheduled for surgery. As with Study CLCT-002, investigators could enroll up to 10% of patients who did not meet the nausea-prone criteria, but were thought to be at risk for developing OINV based on clinical judgment.

Patients were administered one dose at randomization, followed by one dose every 4-6 hours on a fixed schedule for the first 24 hours, then prn as outpatients for Days 2-5. (This contrasts with the earlier study, CLCT-002, where patients were administered one dose at randomization, followed by one dose as needed (prn) every 4-6 hours for up to five days.) Supplemental medications for pain (ibuprofen) or nausea/vomiting (antiemetic of choice) were permitted at any time. Eight days after surgery, subjects returned to clinic for end-of-study assessments.

For analgesia, the primary outcome measure was the PI-NRS, collected at baseline, every 10 minutes until hour two, then every 30 minutes until hour six, and then every hour while awake until 48 hours. The primary endpoint for each subject was the time-weighted sum of pain intensity differences over 48 hours (SPID48). The primary analysis was a comparison of the SPID48 scores between the Hydexor and placebo groups.

For OINV, the primary outcome measure was a responder analysis with responder status derived from the previously requested two criteria. OINV was evaluated using a nausea score, presence of vomiting recorded on a vomiting scale, and requirement for antiemetic medication. Nausea was assessed with the Nausea Intensity Scale (NIS), an 11-point numerical rating scale. On the NIS, the patient was to report the worst nausea they experienced in the past hour from 0 to 10, where a score of 0=no nausea and 10=severe nausea. Vomiting was recorded using the Vomiting Frequency Scale (VFS) where a patient reported how many incidents of vomiting they had in the last hour. For the VFS, a score of 0=no vomiting, 1=one incident in the last hour, 2=two incidents in the last hour, and 3=three or more incidents in the last hour.

For the protocol-specified analysis of OINV, patients were considered responders if they met the following criteria during the first 48 hours of the study:

- Did not report any vomiting
- Did not require the use of antiemetic medication

The pre-specified key secondary outcomes were as follows:

1. The three-component opioid-induced nausea and vomiting endpoint used for the primary endpoint in Study CLCT-003;

2. The use of antiemetics, comparing Hydexor to Norco over 5 days;
3. The occurrence of vomiting, comparing Hydexor to Norco over 5 days;
4. The severity of opioid-induced nausea, comparing Hydexor to Norco over 5 days;
5. The relief of severe pain, comparing Hydexor to Norco over 24 hours (SPID24);
6. Global Evaluation, comparing Hydexor to Norco over 48 hours;
7. Percent change in Qualities of Pain Index (QPI) score over 24 hours, comparing Hydexor to Norco over 24 hours;
8. Incidence of post-discharge nausea and vomiting (PDNV), comparing Hydexor to Norco over days 3-5.

### Statistical Methodology

For this study the null hypothesis for both the analgesia and opioid-induced nausea/vomiting primary endpoints must be rejected in order for the trial to be considered a success. Consequently, no alpha is required for the primary endpoints. The key secondary endpoints were tested using the Hochberg step-up procedure. The statistical methodologies used in the analyses for this study were as follows:

*Analysis of the analgesia primary efficacy endpoint:* This endpoint was analyzed using a linear model with treatment arm, site ID, and baseline pain as covariates. Missing data prior to the first rescue medication or early withdrawal will be replaced with the last prior observation. Observations within 6 hours following rescue medication will be replaced with the baseline observation, and missing data following early withdrawal will be replaced with the baseline observation.

*Analysis of the opioid-induced nausea and vomiting primary efficacy endpoint:* This endpoint was analyzed using a logistic regression model with treatment, investigator, and baseline nausea-prone status as main effects. The three-component version of the endpoint was also analyzed using the same approach.

*Analysis of the key secondary endpoints:* Continuous variables will be analyzed using a linear model. Binary variables will be analyzed using a logistic regression model. All models will include treatment group and the same covariates used in the models for the corresponding primary endpoints.

As for Study CLCT-002, the FDA statistical reviewer performed several exploratory analyses to investigate the observed nausea/vomiting event rates in patients with different response patterns on the screening NPQ.

### Patient Demographics and Patient Disposition

A total of 552 patients were randomized in the trial. The mean age was about 42 years as would be expected for this surgical procedure. The majority of patients (88%) were female and the majority of patients were white (88%). The demographic and other background characteristics were comparable between the two treatment groups.

**Patient Disposition, Study CLCT-003**

<b>Parameter/Category</b>	<b>CL-108 (N=252)</b>	<b>Norco (N=250)</b>	<b>Placebo (N=50)</b>	<b>Total (N=552)</b>
<b>Number of Patients</b>				
Screened				922
Randomized	252	250	50	552
Completed Study [n (%)]	249 (98.8%)	241 (96.4%)	47 (94.0%)	537 (97.3%)
Discontinued Study [n (%)]	3 (1.2%)	9 (3.6%)	3 (6.0%)	15 (2.7%)
<b>Primary Reason for Discontinuation [n (%)]</b>				
Withdrawal of Consent	0	3 (1.2%)	1 (2.0%)	4 (0.7%)
Adverse Event	0	1 (0.4%)	0	1 (0.2%)
Non-Compliance	2 (0.8%)	0	0	2 (0.4%)
Lack of Efficacy	1 (0.4%)	2 (0.8%)	1 (2.0%)	4 (0.7%)
Other	0	3 (1.2%)	1 (2.0%)	4 (0.7%)

Source: FDA Statistical Review

The results of the nausea-prone assessment for all screened patients are shown in the table below. The majority of the patients who completed the nausea-prone assessments met the Sponsor's nausea-prone criteria. Only 26% of those screened did not.

**Results of the Nausea-Prone Assessment for Screened Patients, Study CLCT-003**

<b>Category</b>	<b>N (%)</b>
Likely Nausea-Prone	500 (54%)
Possibly Nausea-Prone	183 (20%)
Not Nausea-Prone	239 (26%)
Total	922

Source: FDA Statistical Reviewer

The table below shows the number and percentage of patients who were randomized into the study that fell into each of the nausea-prone groupings. The study allowed up to 10% of patients that did not meet the predefined nausea-prone criteria to be enrolled into the study based on investigator discretion. Ninety-three percent (93%) of the patients randomized into the study were considered nausea-prone (possibly or likely) and 7% were enrolled based on investigator discretion.

**Results of the Nausea-Prone Assessments for Randomized Patients, CLCT-003**

<b>Category</b>	<b>N (%)</b>
Likely Nausea-Prone	383 (69%)
Possibly Nausea-Prone	132 (24%)
Investigator Discretion	37 (7%)
Total	552

Source: FDA Statistical Reviewer



## Results

*Analgesia Endpoint:* For the primary analysis, the following table shows the Sponsor's results. Patients in the Hydexor (CL-108) treatment arm were found to have statistically significantly greater reductions in pain intensity over the first 48 hours of the study than patients in the placebo arm. Again, Hydexor was not compared to Norco, as promethazine was not expected to contribute to the analgesic effect.

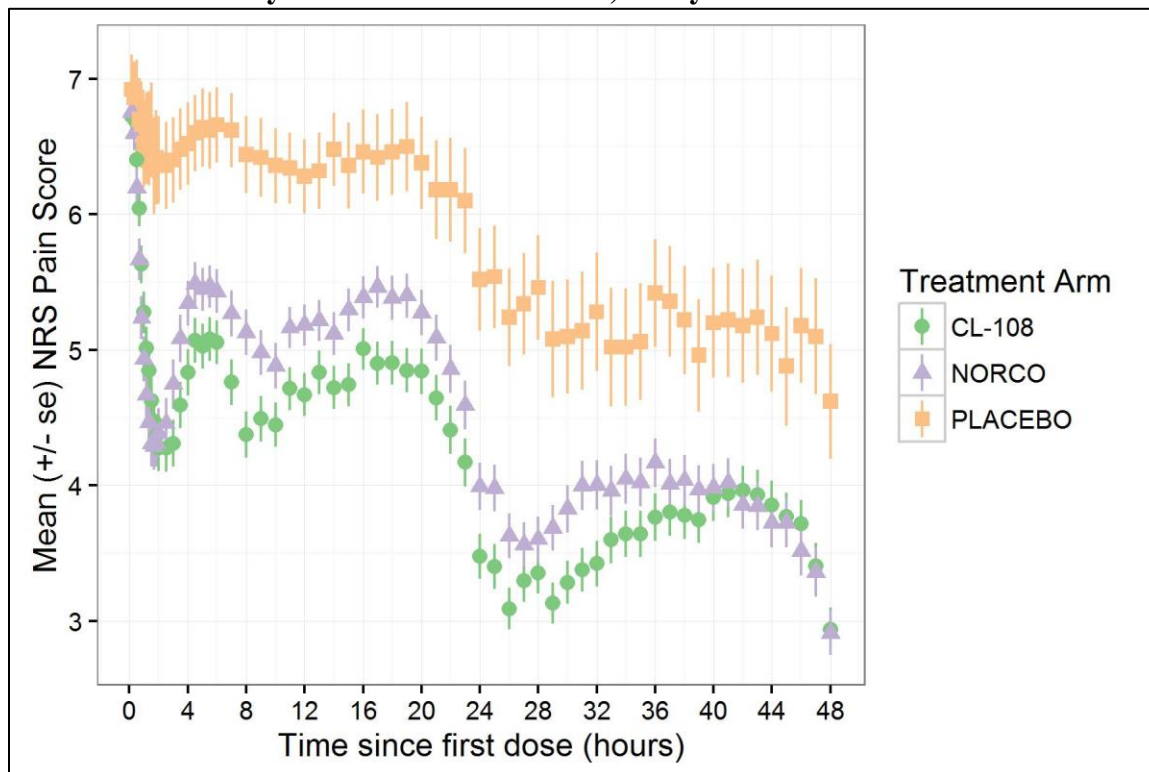
### Primary Analysis Results, Study CLCT-003, Sponsor

Endpoint	Estimate P-Value	CL-108 (N=252)	Norco (N=250)	Placebo (N=50)
<b>Analgesia Endpoint:</b>				
<b>SPID<sub>48</sub></b>				
N		252	250	50
Mean (SD)		118.4 (80.02)	107.0 (83.60)	53.1 (69.69)
Median		109.5	88.0	32.3
Min, Max		-23, 399	-12, 380	-79, 313
<b>CL-108 vs Placebo</b>				
LS-Means Difference	69.2			
(95% CI)	(45.9, 92.5)			
P-Value	<0.001			

Source: FDA Statistical Review

The figure below shows a plot of the mean pain intensity over the first 48 hours of the study with clear separation of both CL-108 and Norco from placebo.

### Mean Pain Intensity over the First 48 Hours, Study CLCT-003



Source: FDA Statistical Review

The table below shows the use of rescue medication. The use of rescue medication was similar for the CL-108 and Norco treatment arms and was lower in both cases than for placebo. The use of rescue medication was not included as one of the key secondary endpoints and no statistical tests were performed.

### Rescue Use by Treatment Arm, Study CLCT-003

Rescue Medication	Rescue Medication Use	CL-108 (N=252)	Norco (N=250)	Placebo (N=50)
Ibuprofen	Number (%)	169 (67%)	176 (70%)	50 (100%)
	Mean Dose (mg) among patients requiring rescue	1207	1180	1960
Ketorolac	Number (%)	35 (14%)	39 (16%)	22 (44%)
	Mean Dose (mg) among patients requiring rescue	38	47	61

Source: FDA Statistical Review

*OINV Endpoint:* The Sponsor’s results for both the protocol-specified primary analysis and the key secondary analysis are shown in the table below. The comparisons are between the Hydexor and Norco treatment arms of the study. There was a statistically significant reduction in the percentage of responders by both definitions for CL-108 compared to Norco.

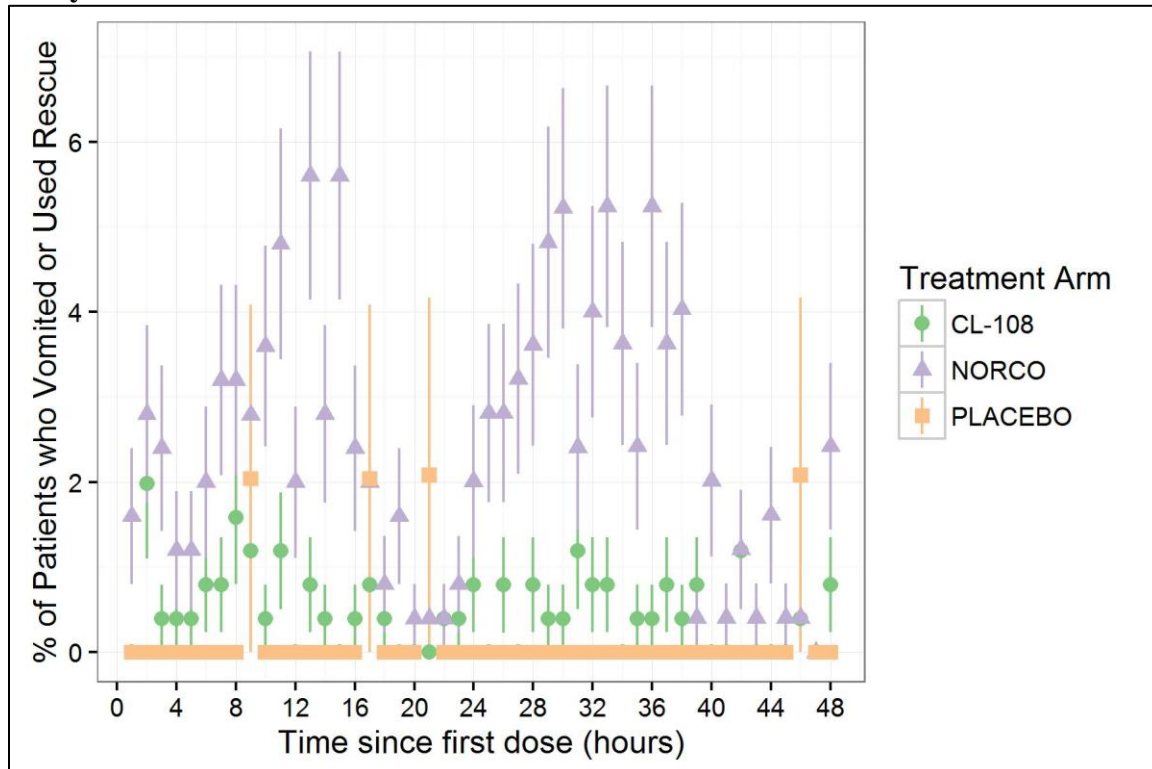
**Assessment of the OINV Study Endpoints, Study CLCT-003**

Endpoint	CL-108 (N=252)	Norco (N=250)	Placebo (N=50)	Relative Risk Reduction	Odds Ratio (95% CI)	P-Value
Two Component OINV Failures (Primary)	30 (12%)	113 (45%)	3 (6%)	74%	0.16 (0.10, 0.25)	<0.001
Three Component OINV Failures (Key Sec.)	68 (27%)	135 (54%)	8 (16%)	50%	0.31 (0.21, 0.45)	<0.001

Source: FDA Statistical Review

The between-group differences for the occurrence of vomiting or anti-emetic rescue use are demonstrated in the following graph.

**Percentage of Patients Vomiting or Using Anti-Emetic Rescue over the Previous Hour, Study CLCT-003**



Source: FDA Statistical Reviewer

The results for all key secondary endpoints are summarized in the following two tables. Six of the eight analyses were statistically significant after using the Hochberg step-up procedure, as pre-specified in the analysis plan.

**Key Secondary Endpoints Analyzed using Logistic Regression, Study CLCT-003**

<b>Endpoint</b>	<b>Odds Ratio (95% CI)</b>	<b>Relative Risk</b>	
		<b>Reduction (95% CI)</b>	<b>P-Value vs Norco</b>
Occurrence of Nausea/Vomiting (3-Component) over 48 hours	0.31 (0.21, 0.45)	50.0 (34.7, 65.3)	< 0.001*
Use of any Anti-Emetics over 5 Days	0.18 (0.12,0.28)	70.7 (54.4, 86.9)	< 0.001*
Occurrence of Vomiting over 5 Days	0.28 (0.16, 0.48)	65.8 (39.9, 91.8)	< 0.001*

Source: FDA Statistical Review

Note: \* indicates a statistical significant difference after using the Hochberg step-up procedure

**Key Secondary Endpoints Analyzed using a Generalized Linear Model, Study CLCT-003**

<b>Endpoint</b>	<b>LS-Mean</b>	
	<b>Difference (95% CI)</b>	<b>P-Value vs Norco</b>
Severity of Opioid Induced Nausea (NIS & WNS) over 5 Days	-95.5 (-119.2, -71.7)	< 0.001*
Relief of Severe Pain over 24 Hours (SPID24) for Patients with PI-NRS > 7 at Baseline	13.4 (3.0, 23.8)	0.012*
Physician Global Evaluation (PGE) over 48 hours	0.4 (0.0, 0.7)	0.032
% Change in Overall QPI Score over 24 Hours	-5.8 (-13.2, 1.5)	0.117
Number of Incidents of Post-Discharge Nausea and Vomiting	0.37 (0.32, 0.42)	< 0.001*

Source: FDA Statistical Review

Note: \* indicates a statistical significant difference after using the Hochberg step-up procedure

The table below shows the number and percentage of patients who met the two-component OINV criteria, which was used as the primary analysis, broken down by treatment group and nausea-prone classification. In the active treatment groups, patients that were classified as likely nausea-prone (history of OINV) failed the two-component OINV criteria at slightly higher rates than patients who were classified as being possibly nausea-prone.

### Percentage of Two-Component OINV Failures, Study CLCT-003

<b>Nausea-Prone Category</b>	<b>CL-108 (N=252)</b>	<b>Norco (N=250)</b>	<b>Placebo (N=50)</b>
Likely Nausea-Prone	25/175 (14%)	85/172 (49%)	3/36 (8%)
Possibly Nausea-Prone	5/63 (8%)	22/58 (38%)	0/11 (0%)
Investigator Discretion	0/14 (0%)	6/20 (30%)	0/3 (0%)

Source: FDA Statistical Reviewer

Regardless of the nausea-prone classification at screening, the magnitude of reduction in OINV events for CL-108 compared to Norco appears to be similar (Likely Nausea-Prone: 35%, Possibly Nausea-Prone: 30%, Investigator Discretion: 30%).

### Subgroup Analyses

Analyses by age, sex, and race showed similar results for both the analgesia and OINV outcomes for sex and race. Too few patients 65 years or older were enrolled in either Phase 3 study to allow any meaningful conclusions about the effect of age on overall efficacy for analgesia or OINV.

### **Discussion**

The results from the analysis of the data from each study demonstrated statistically significant improvement in pain when compared to placebo and a statistically significant reduction in OINV when compared to Norco regardless of how the OINV endpoint was defined. Both studies actively enriched and only enrolled patients who were more likely to experience nausea and vomiting. Consequently, it is not possible to extrapolate the effectiveness of this product to patients who are not expected to be prone to nausea and vomiting.

DGIEP reviewed the efficacy data and concurred that less OINV was observed with Hydexor than Norco in the two efficacy studies. DGIEP noted that “[w]hile the primary efficacy assessment time point was 24 hours for Study CLCT-002 and 48 hours for Study CLCT-003, CR [complete response, defined as no emetic episode and no use of rescue medication] rates were measured in each treatment group on each day of the 5-day study period. In Study CLCT-002, the difference in CR rate (preferred DGIEP endpoint, post-hoc analysis) between the CL-108 and Norco treatment groups was found to be nominally statistically significant out to 96 hours. In Study CLCT-003, the difference was found to be nominally statistically significant for each of the five study days ( $p < 0.001$ )... These results provide information to support the durability of the efficacy of CL-108 for the prevention of OINV for up to 5 days.”

DGIEP also noted that, based on effects on the preferred OINV outcome, antiemetic products generally carry the indication “prevention of nausea and vomiting” and do not include “reduction of nausea and vomiting,” as proposed by the Sponsor.

## 4. Clinical Safety

The safety profile of HC/acetaminophen in combination and promethazine are well-characterized, as reflected in approved labeling for hydrocodone/acetaminophen and promethazine (refer to appendices). Therefore, the safety review for this application focused on the safety of these three drugs used in combination with particular emphasis on central nervous system depressant effects because of this shared risk between opioids and antihistamines. The safety data submitted in the NDA are derived from five clinical studies. CLCT-004 was a Phase 1 bioavailability study. Studies CLCT-002 and 003 were the two Phase 3 efficacy studies. Study CLCT-006 was a Phase 3 open-label safety study in patients with osteoarthritis of the knee or hip. CLCT-007 was a human abuse-liability study to assess the abuse potential of the new combination.

The three Phase 3 efficacy and safety studies each had a different dosing regimen. In CLCT-002, patients were administered one dose at randomization, followed by one dose as needed (prn) every 4-6 hours for up to five days. In CLCT-003, patients were administered one dose at randomization, followed by one dose every 4-6 hours on a fixed schedule for the first 48 hours, then prn on an outpatient basis for Days 3-5. In CLCT-006, patients were administered one dose prn every 4-6 hours for up to fourteen days.

Safety endpoints discussed in the Clinical Review include the following:

- Incidence and severity of AEs based on spontaneous reporting
- Incidence and severity of nine expected opioid-induced AEs based on proactive monitoring with the Opioid Symptoms Scales (OSS) in Studies CLCT-002 and CLCT-003; the nine AEs included confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizziness (OINV was not measured on the OSS, but was measured as an efficacy measure in the two Phase 3 efficacy studies); for each opioid symptom, patients completed separate 0-to-10 Likert scales in response to the instruction: “For each symptom you’ve had over the past 6 hours (or 24 hours), circle the number that describes how severe it was for you.”
- Vital signs collected in CLCT-002, CLCT-003, CLCT-006, and CLCT-004
- Electrocardiograms (ECGs) collected in CLCT-006, CLCT-004, and CLCT-007; ECGs were not collected in the two Phase 3 efficacy studies
- Laboratory assessments collected in CLCT-006 and CLCT-004 (lab testing in CLCT-006 did not include liver function tests); labs were not collected in the two Phase 3 efficacy studies

A total of 709 individuals were exposed to at least one dose of the to-be-marketed formulation of Hydexor. A total of 463 patients were treated with Hydexor across the two Phase 3 efficacy studies. A total of 641 patients were treated with Hydexor across all Phase 3 studies, including the two efficacy studies and Study CLCT-006 (patients with osteoarthritis of the knee or hip).

Also, 48 subjects received a higher single dose of Hydexor, either three or five tablets as a single dose, as part of the human abuse-potential study, Study CLCT-007.

The following tables summarize the exposures across the two different pools.

**Duration of Exposure Across the Phase 3 Efficacy Studies**

<b>Duration of Exposure (Days)</b>	<b>CL-108</b>	<b>Norco® (N=455)</b>	<b>Placebo</b>
At least 1 day	463 (100)	455 (100)	100 (100)
At least 3 days	441 (95.2)	407 (89.5)	84 (84.0)
At least 5 days	338 (73.0)	290 (63.7)	58 (58.0)
At least 7 days	17 (3.7)	18 (4.0)	2 (2.0)

Source: Clinical Review

### Duration of Exposure Across All Phase 3 Studies

Duration of Exposure Days	CL-108 (N=641)	Norco® (N=455)	Placebo (N=100)
At least 1 day	641 (100)	455 (100)	100 (100)
At least 3 days	617 (96.3)	407 (89.5)	84 (84.0)
At least 5 days	511 (79.7)	290 (63.7)	58 (58.0)
At least 7 days	187 (29.2)	18 (4.0)	2 (2.0)
At least 14 days	153 (23.9)	0	0

Source: Clinical Review

In the tables above, a patient would contribute to exposure on a given day based on the consumption of a single tablet of study drug. Only Study CLCT-003 required that patients take Hydexor at the maximally proposed dosing regimen of every 4-6 hours. This was a requirement for the first 48 hours of the study. In the tables above, exposures on days beyond 48 hours consist mostly of patients taking three or fewer tablets on a given day.

Patients administered the maximally-allowed number of tablets per day would receive about 5-6 tablets per day. In Study CLCT-003, about 40% of patients received 5-6 tablets per day for the first and second days. In the same study, the average number of tablets per day dropped off to 3 for the third day, 2.6 for the third day, and 2 for the fifth day. As will be seen below, the number of tablets taken per day had a noticeable effect on the occurrence and severity of some adverse events (AEs), especially drowsiness, in Study CLCT-003.

The demographics for the population of patients enrolled across all three Phase 3 studies is shown in the table below. Note that Study CLCT-006 significantly increased the number of patients  $\geq 65$  years that were exposed to Hydexor.

### Demographics of Pooled Patient Population, Studies CLCT-002, -003, and -006

Parameter	CL-108 (N=641)	Norco® (N=455)	Placebo (N=100)
Age at Baseline (Years)			
Mean (SD)	40.6 (18.35)	33.0 (14.28)	32.0 (13.96)
Median	38.0	27.0	26.0
Q1, Q3	23.0, 57.0	21.0, 45.0	20.0, 44.0
Min, Max	18, 86	18, 68	18, 62
Age Subgroups at Baseline (n, [%] )			
<65 Years	568 (88.6)	449 (98.7)	100 (100.0)
$\geq 65$ Years	73 (11.4)	6 (1.3)	0
Gender (n, [%])			
Male	151 (23.6)	84 (18.5)	25 (25.0)
Female	490 (76.4)	371 (81.5)	75 (75.0)
Race (n, [%])			
White	536 (83.6)	389 (85.5)	84 (84.0)
Black or African American	67 (10.5)	30 (6.6)	10 (10.0)
Asian	18 (2.8)	19 (4.2)	5 (5.0)
Other	20 (3.1)	17 (3.7)	1 (1.0)

Source: Clinical Review



### Serious Adverse Events (SAEs)

There were no SAEs that were attributed to Hydexor.

### Discontinuations Due to AEs

There were no discontinuations due to AEs from the Hydexor groups in the Phase 3 efficacy studies. In Study CLCT-006, there were three such discontinuations. One was a fall two days after the last dose of Hydexor in an 84-year-old woman. One was a case of moderate nausea with mild hyperhidrosis. One patient experienced severe abdominal discomfort, diarrhea, somnolence, and tachycardia. All the events resolved after Hydexor discontinuation.

### Opioid-Induced Side Effects

The incidence and severity of nine expected opioid-induced AEs was based on proactive monitoring with the Opioid Symptoms Scales (OSS). The nine AEs included in the OSS were confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizziness. OINV was not measured on the OSS, but was rather measured as an efficacy measure in the two Phase 3 efficacy studies and is summarized in the efficacy summary of this document. For each opioid symptom, patients completed separate 0-to-10 Likert scales in response to the instruction: “For each symptom you’ve had over the past 6 hours (or 24 hours), circle the number that describes how severe it was for you.”

Patients completed the OSS questionnaire before and regularly after repeated uses of assigned study medication over 5 days in CLCT-002 and CLCT-003. Subjects rated each symptom, on a 0-10 point scale (rating severe events between 7-10, moderate events between 4-6, mild events 1-3, and no symptoms as 0), before taking study medication. In CLCT-002, patients completed the OSS pre-treatment, at the end of the 6-hour initial evaluation period, and nightly for the five-day treatment period. In CLCT-003, the OSS was completed by patients at the end of the initial 6-hour evaluation period, at 24 and 48 hours in-clinic, and nightly on Days 3, 4, and 5.

Likely due in part to the active surveillance for these side effects, the observed background rates in the placebo group were relatively high. For example, background rates (any severity) were 77%, 69%, 36%, 36%, and 35% respectively for headache, drowsiness, difficulty concentrating, itchiness, and lightheadedness/dizziness. In contrast, the spontaneously-reported incidence of drowsiness in the Hydexor-treated patients in Study CLCT-006 was only 18%.

In Study CLCT-003, patients were required to take one dose of study medication every 4-6 hours for 48 hours and the average number of doses per day was 4.7. This was in contrast to Study CLCT-002 where patients self-dosed as needed and the average number of doses per day was 2.5. As a result, the incidence of AEs in the pooled efficacy studies represents a range of exposure to drug.

The following table shows the OSS results for the pooled efficacy studies.

### OSS Opioid-Induced Symptoms in the Pooled Efficacy Studies

OSS Rating	Opioid-Induced Symptom	CL-108 (N=463)	Norco (N=455)	Placebo (N=100)
Mild, Moderate or Severe (OSS Rating = 1-10)	Confusion	149 (32.2%)	106 (23.3%)	10 (10.0%)
	Constipation	205 (44.3%)	216 (47.5%)	20 (20.0%)
	Difficulty Concentrating	241 (52.1%)	206 (45.3%)	36 (36.0%)
	Difficulty Voiding	47 (10.2%)	38 (8.4%)	6 (6.0%)
	Drowsiness	431 (93.1%)	403 (88.6%)	69 (69.0%)
	Dry Mouth	331 (71.5%)	288 (63.3%)	53 (53.0%)
	Headache	328 (70.8%)	328 (72.1%)	77 (77.0%)
	Itchiness	251 (54.2%)	239 (52.5%)	36 (36.0%)
	Lightheaded/Dizzy	303 (65.4%)	303 (66.6%)	35 (35.0%)

Source: Clinical Review

For the pooled efficacy studies, over the 5-day treatment period, the mean severity of most opioid side effects was rated as mild (1-3 on the 0-10 OSS) in the CL-108 and Norco groups. The exception was drowsiness, which was rated as mild by 77 subjects (16.6%), moderate (4-6 on the OSS) by 143 subjects (30.9%), and severe (7-10 on the OSS) by 211 subjects (45.6%). Severe drowsiness was reported by 46% of Hydexor-treated patients and by 29% of Norco-treated patients.

### OSS Results in Study CLCT-002

The proportion of subjects with at least one severe symptom (rated 7-10 on the OSS questionnaire) over the 5 days of the study was 54.0% (114 subjects) in the CL-108 group and 52.2% (107 subjects) in the Norco treatment group as shown in the table below. However, drowsiness was the most commonly reported severe side effect following CL-108 treatment and Norco treatments, affecting 46% (97 subjects) of subjects and 37.1% (76 subjects), respectively.

### Summary of the Severe OSS Opioid-induced Symptoms Over 5 Days (Study CLCT-002)

Opioid-Induced Symptom	CL-108 (N=211)	Norco <sup>®</sup> (N=205)	Placebo (N=50)
Total Number of Severe OSS Opioid-Induced Symptoms	664	423	61
Number of Subjects with at Least One Severe OSS	114 (54.0)	107 (52.2)	20 (40.0)
Confusion	14 (6.6)	5 (2.4)	0
Constipation	17 (8.1)	23 (11.2)	2 (4.0)
Difficulty Concentrating	25 (11.8)	18 (8.8)	4 (8.0)
Difficulty Voiding	4 (1.9)	1 (0.5)	0
Drowsiness	97 (46.0)	76 (37.1)	8 (16.0)
Dry Mouth	26 (12.3)	15 (7.3)	3 (6.0)
Headache	41 (19.4)	36 (17.6)	14 (28.0)
Itchiness	11 (5.2)	11 (5.4)	0
Lightheaded/Dizzy	41 (19.4)	37 (18.0)	3 (6.0)

Source: Clinical Review

### OSS Results in Study CLCT-003 (Fixed Dosing for 48 Hours, Followed by As-Needed Dosing)

Over the entire 5-day treatment period, there was no difference in the number of subjects reporting constipation, headache, lightheadedness, difficulty voiding, and itchiness for CL-108 when compared to those treated with Norco as shown in the table below. However, there were more occurrences of drowsiness, confusion, difficulty concentrating, and dry mouth with CL-108 treatment than in the Norco treatment group.

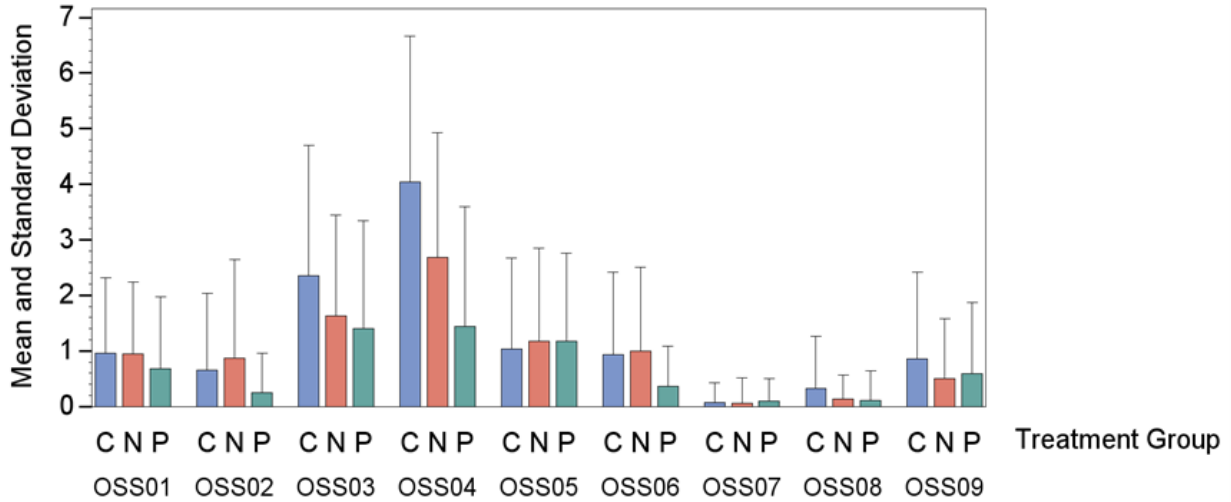
#### Summary of the Severe OSS Opioid-induced Symptoms

Opioid-Induced Symptom	CL-108 (N=252)		Norco (N=250)		Placebo (N=50)	
	Days 1-2	Days 3-5	Days 1-2	Days 3-5	Days 1-2	Days 3-5
Total Number of Severe OSS Opioid-Induced Symptoms	389	276	222	157	29	4
Number of Subjects with at Least One severe OSS	125 (49.6)	83 (32.9)	88 (35.2)	54 (21.6)	10 (20.0)	3 (6.0)
Confusion	6 (2.4)	2 (0.8)	0	1 (0.4)	0	0
Constipation	16 (6.3)	30 (11.9)	18 (7.2)	35 (14.0)	2 (4.0)	1 (2.0)
Difficulty Concentrating	20 (7.9)	7 (2.8)	8 (3.2)	3 (1.2)	2 (4.0)	0
Difficulty Voiding	1 (0.4)	0	2 (0.8)	1 (0.4)	0	0
Drowsiness	105 (41.7)	46 (18.3)	53 (21.2)	12 (4.8)	4 (8.0)	0
Dry Mouth	38 (15.1)	31 (12.3)	17 (6.8)	5 (2.0)	4 (8.0)	0
Headache	27 (10.7)	19 (7.5)	27 (10.8)	14 (5.6)	6 (12.0)	0
Itchiness	15 (6.0)	13 (5.2)	11 (4.4)	9 (3.6)	1 (2.0)	1 (2.0)
Lightheaded/Dizzy	18 (7.1)	12 (4.8)	19 (7.6)	9 (3.6)	1 (2.0)	1 (2.0)

Source: Clinical Review

For Study CLCT-003, the severity of the nine targeted opioid-related symptoms is shown in the following graph.

**Severity of Opioid-Related Symptoms (11-Point Intensity Rating Scale; Mean and Standard Deviation) over First 48 Hours (excluding OINV), Study CLCT-003**

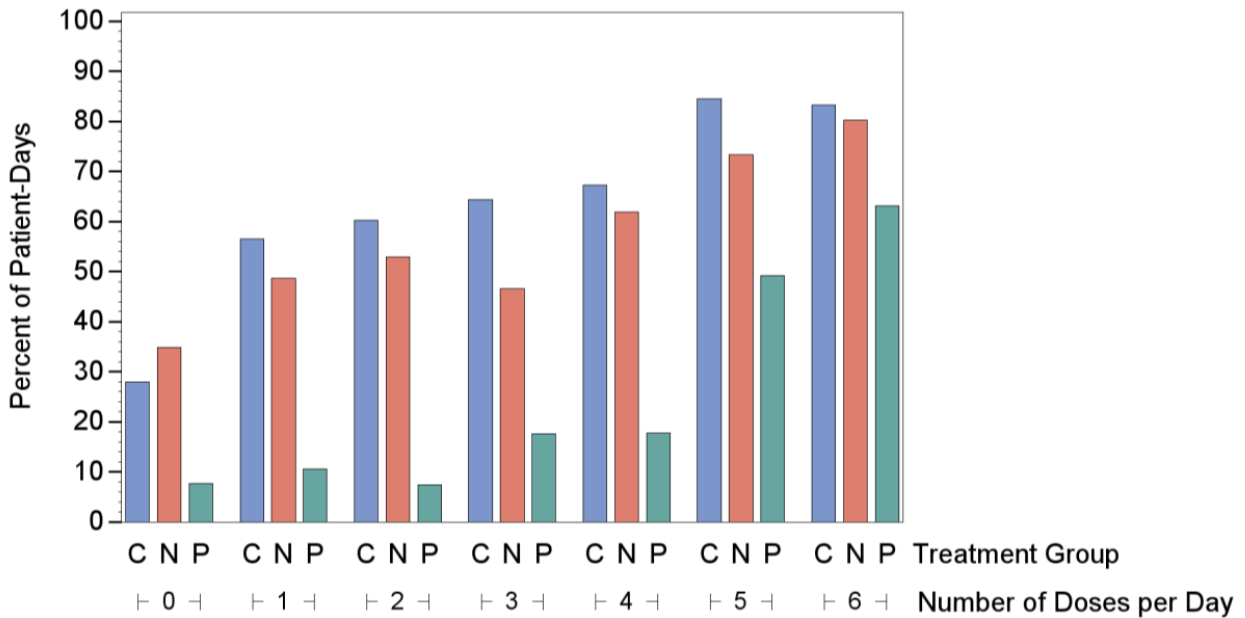


Treatment Group: C = CL-108, N = Norco, P = Placebo.  
 OSS01 = Itchiness, OSS02 = Constipated, OSS03 = Dry Mouth, OSS04 = Drowsy, OSS05 = Headache,  
 OSS06 = Lightheaded/Dizzy, OSS07 = Difficult to Pass Urine, OSS08 = Confused,  
 OSS09 = Difficult to Concentrate.

Source: Clinical Study Report, Study CLCT-003

Over the first five days of the study, the incidence of moderate-severe drowsiness was greater with Hydexor (75%) than with Norco (56%). The following figures demonstrate that both the incidence and severity of drowsiness were related to the number of doses taken per day.

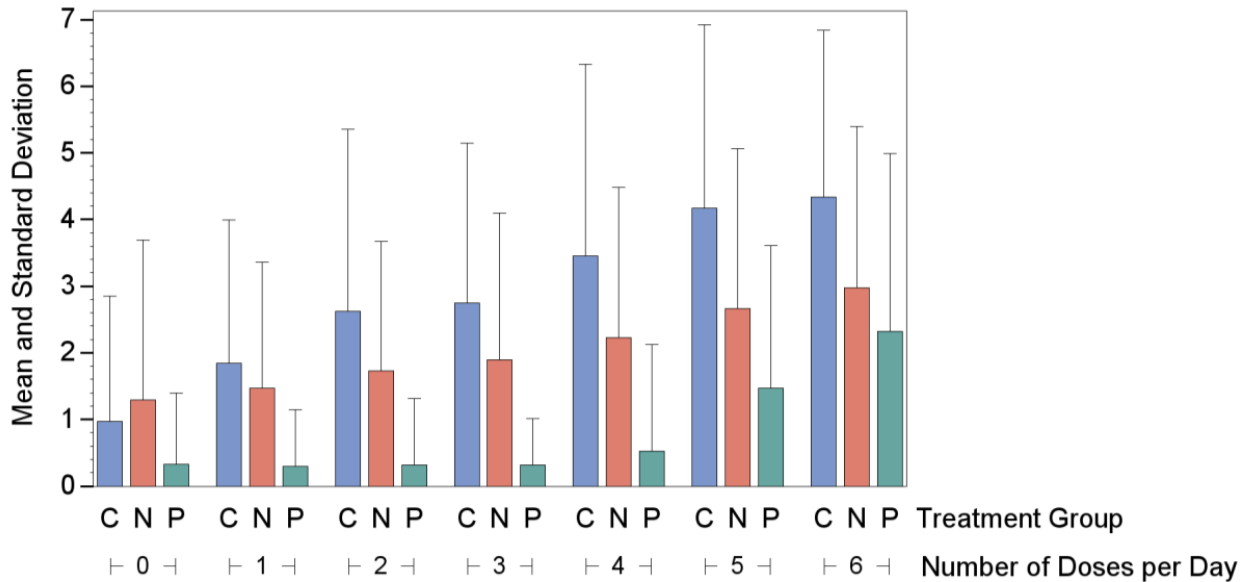
**Frequency of Drowsiness versus Number of Doses per Day, Study CLCT-003**



Treatment Group: C = CL-108, N = Norco, P = Placebo.

Source: Clinical Study Report, Study CLCT-003

**Severity of Drowsiness (11-Point Intensity Rating Scale; Mean and Standard Deviation) versus Number of Doses per Day, Study CLCT-003**



Treatment Group: C = CL-108, N = Norco, P = Placebo.

Source: Clinical Study Report, Study CLCT-003

At comparable dosing regimens, there was an excess in the frequency and severity of drowsiness with Hydexor compared to Norco.

Safety Considerations of Special Interest

In the Integrated Summary of Safety, the Sponsor identified a number of events of special interest with the new drug combination and they include the following.

*Respiratory*

There was one report of dyspnea in a Hydexor-treated patient. The event was reported on study day two, was mild, and considered unlikely related to drug. No change in study drug occurred as a result of this event and the patient completed the treatment period without recurrence. There was no evidence of an increased risk of respiratory depression with Hydexor compared to Norco.

*Hypotension and Syncope*

In the pooled data for CLCT-002 and CLCT-003, AEs of hypotension were reported in two (0.4%) subjects in the Hydexor group, two (0.4%) subjects in the Norco group, and one (1.0%) subject in the placebo group. These five events occurred in five subjects in Study CLCT-003. One AE of blood pressure decreased was reported in one (0.2%) subject in the Hydexor group and in one (0.2%) subject in the Norco group. These two events occurred in two subjects in Study CLCT-002.

In the pooled data for CLCT-002 and CLCT-003, AEs of syncope were reported in five (1.1%) subjects in the Hydexor group, in no subjects in the Norco group, and in one (1.0%) subject in the placebo group. These five events occurred in four subjects in CLCT-003 and in one subject

in CLCT-002. There were no reported cases of syncope in CLCT-006. None of the cases of syncope were SAEs and all recovered without recurrence and continued in the study. Review of the narratives provided for the eight cases of syncope/presyncope in Hydexor-treated patients did not raise any additional concern.

None of the blood pressure-related AEs in Hydexor-treated patients were rated severe. Vital sign data is discussed below (see Vital Signs section) and showed a signal for a greater effect of Hydexor than Norco to lower blood pressure.

#### *Temperature Elevations*

Neuroleptic Malignant Syndrome has been reported in association with promethazine alone or in combination with antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic dysfunction. There were no AEs reported in any of the subjects who experienced pyrexia in the CL-108 studies that would be consistent with Neuroleptic Malignant Syndrome, including mental status change, muscle rigidity, or autonomic dysfunction.

There were reports of pyrexia in Studies CLCT-002 and CLCT-003, but this is not unexpected in a population of postsurgical patients. Across the pooled studies, the incidence of pyrexia and/or body temperature increased appeared to be as common in the placebo group as in the Hydexor group. In the pooled data for CLCT-002 and CLCT-003, AEs of pyrexia were reported in five (1.1%) subjects in the Hydexor group, one (0.2%) subject in the Norco group, and three (3.0%) subjects in the placebo group. AEs of body temperature increased were reported in six (1.3%) subjects in the Hydexor group and in no subjects in the Norco or placebo groups. All but two of the events were mild. The remaining two events were moderate.

Only one event of pyrexia was reported in Study CLCT-006. The event was mild and lasted three days, resolving without sequelae.

#### Common Adverse Events

The following table shows the common AEs for the pooled Phase 3 efficacy studies, excluding OINV and the nine OSS AEs. Pyrexia, body temperature increased, and syncope have already been discussed in more detail above. Pyrexia occurred more frequently in the placebo group than the Hydexor group. Syncope occurred in about 1% of patients in both the Hydexor and placebo groups.

## Common (>1%) Adverse Events in the Pooled Efficacy Studies, Excluding OINV and OSS Symptoms

System Organ Class Preferred Term <sup>a</sup>	CL-108 (N=463)	Norco® (N=455)	Placebo (N=100)
Total Number of TEAEs	50	60	42
Number of Subjects with at Least One TEAE	49 (10.6)	54 (11.9)	28 (28.0)
Gastrointestinal disorders			
Abdominal pain upper	2 (0.4)	5 (1.1)	1 (1.0)
General disorders and administration site conditions			
Pyrexia	5 (1.1)	1 (0.2)	3 (3.0)
Infections and infestations			
Alveolar osteitis	8 (1.7)	17 (3.7)	2 (2.0)
Investigations			
Body temperature increased	6 (1.3)	0	0
Metabolism and nutrition disorders			
Decreased appetite	0	8 (1.8)	0
Nervous system disorders			
Syncope	5 (1.1)	0	1 (1.0)

Source: Clinical Review

The common AEs observed in Study CLCT-006 do not add to the characterization of the safety profile of Hydexor. It is worth noting the absence of syncope, pyrexia, and temperature elevations among the common AEs in CLCT-006, despite their occurrence in the two efficacy studies.

### Vital Signs

Vital signs were collected in Studies CLCT-002, CLCT-003, and CLCT-006. Blood pressure, pulse, respiratory rate, oxygen saturation, and temperature were assessed.

The mean change in sitting diastolic blood pressure (DBP) from baseline to six hours post-dose was -7.4 mm Hg for Hydexor, -5.1 mm Hg for Norco, and -2.7 mm Hg for placebo. The percentage of subjects with potentially clinically significant (PCS) abnormalities of low DBP (defined as  $\leq 50$  mm Hg and  $\geq 15$  mm Hg decrease from baseline) was greater in the Hydexor group compared to the Norco group from three hours to six hours post-dose. In Study CLCT-003 alone (with fixed dosing), the percentages of Hydexor-treated patients with PCS values for low DBP at 6, 12, and 24 hours were 22%, 18%, and 17% respectively versus 14%, 8%, and 17% for Norco-treated patients.

Similar trends in the percentage of subjects with PCS abnormalities of low systolic blood pressure (SBP) (defined as  $\leq 90$  mm Hg and  $\geq 20$  mm Hg decrease from baseline) were observed. In Study CLCT-003 alone (with fixed dosing), the percentages of Hydexor-treated patients with PCS values for low SBP at 6, 12, and 24 hours were 6%, 6%, and 6% respectively versus 3%, 2%, and 2% for Norco-treated patients. The mean change in SBP from baseline to six hours post-dose was -8.9 mm Hg for Hydexor, -6.1 mm Hg for Norco, and -2.2 mm Hg for

placebo.

The signal for a greater effect of Hydexor versus Norco to lower blood pressure is consistent with the AE profile for promethazine and consistent with the alpha-adrenergic blocking effects.

There were some transient abnormalities in respiratory rate and oxygen saturation in both the Hydexor and Norco groups that were consistent with the AE profile for opioids and did not raise additional concern.

In the pooled analysis of body temperature vital signs for Studies CLCT-002 and CLCT-003, there were no findings of high body temperature considered to be potentially clinically significant at any timepoint.

#### Laboratory Findings

Laboratory assessments were not collected in the two Phase 3 efficacy studies. They were collected at baseline and at end-of-study in Study CLCT-006. Blood samples were collected for hematology and chemistry tests. The chemistry testing did not include liver function tests. Urinalysis was also performed. The clinical review does not raise any concerns for drug-induced changes for any of the parameters measured.

#### ECGs

As with the laboratory assessments, ECGs were not collected in the two Phase 3 efficacy studies. They were collected at baseline and at end-of-study in Study CLCT-006. The clinical review does not raise any concern for treatment-emergent ECG changes.

#### **Discussion**

The adverse event profile overall appeared acceptable in the intended to-be marketed dosage of one tablet (hydrocodone 7.5mg/acetaminophen 325mg/promethazine 12/5 mg) every 4-6 hours as needed and was consistent with a mu-opioid agonist, acetaminophen, and promethazine. However, the decrease in gastrointestinal AEs must be weighed against an increase in CNS AEs.

The comparative safety profiles of Hydexor and Norco under the maximally-recommended dosing regimens were characterized in the first 48 hours of Study CLCT-003. In Studies CLCT-002 and CLCT-006, total daily doses were for the most part much less than the maximally-recommended 5-7 tablets per day. As shown above, the incidence and severity of drowsiness was significantly greater for Hydexor than Norco and was related to the number of tablets ingested. While no SAEs resulted during the 48-hour period of Study CLCT-003, it is worth noting that patients were required to stay in the study unit for the first 48 hours of this study, and were subject to careful observation.

In addition to the greater risk of drowsiness, a greater hypotensive effect with Hydexor than Norco has also been characterized. In part, for this reason, the product if eventually approved should be indicated only for patients known to already be at risk for OINV and labeling should include information regarding the increase in drowsiness and decrease in blood pressure associated with Hydexor.



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology Review**

Date: January 11, 2018

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Subject: Review of epidemiologic data on misuse and abuse of hydrocodone and promethazine

Drug Name(s): Hydexor (immediate-release hydrocodone/acetaminophen/promethazine HCL)

Application Type/Number: NDA #209257

Applicant/sponsor: Charleston Laboratories

OSE RCM #: 2017-2119

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## **ABBREVIATIONS**

**AAPCC:** American Association of Poison Control Centers

**ASI-MV:** Addiction Severity Index Multimedia Version

**CDC:** Centers for Disease Control and Prevention

**CNS:** Central Nervous System

**CSA:** Controlled Substances Act

**DIM:** Drug-Involved Mortality

**ED:** Emergency Department

**FDA:** U.S. Food and Drug Administration

**FDC:** Fixed Dose Combination

**ICD-10:** International Statistical Classification of Diseases and Related Health Problems, 10th  
Revision

**NAVIPPRO:** National Addictions Vigilance Intervention and Prevention Program

**NDA:** New Drug Application

**NPDS:** National Poison Data System

**NEISS-CADES:** National Electronic Injury Surveillance System -- Cooperative Adverse Drug  
Event Surveillance

**NSDUH:** National Survey on Drug Use and Health

**OTP:** Opioid Treatment Program

**PCC:** Poison Control Center

**RADARS:** Researched Abuse, Diversion, and Addiction-Related Surveillance

**RMPDC:** Rocky Mountain Poison and Drug Center

**SKIP:** Survey of Key Informants' Patients

**US:** United States

## EXECUTIVE SUMMARY

Hydexor™ is an immediate-release (IR) fixed-dose combination drug product containing hydrocodone bitartrate, acetaminophen, and promethazine hydrochloride. It is not designed with abuse-deterrent properties. Charleston Laboratories has submitted an NDA for Hydexor for the relief of moderate to severe pain while preventing or reducing the opioid induced nausea and vomiting.

In July 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) issued the report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*.<sup>1</sup> The NASEM committee's charge was to help the FDA develop a framework for opioid review, approval, and monitoring that balances individual need for pain control with the broader public health consequences of opioid misuse. The report suggests that such an approach might involve assessing evidence of a product potential for diversion and misuse and predicted risks to family members and society.

The purpose of this epidemiologic review is to provide information to inform the evaluation of the risk-benefit balance of Hydexor for patients when used as directed, as well as considering potential harms to patients or others arising from misuse and abuse. It includes information on the misuse and abuse of both hydrocodone and promethazine and associated morbidity and mortality, drawing from published literature, surveys, poison control center calls, emergency department visit records, death certificates, and internet drug abuse discussion forums.

The epidemiologic data indicate that misuse and abuse of hydrocodone remain widespread in the U.S. Relative to their large prescription volume, however, IR hydrocodone combination product abuse rates are generally lower than for other prescription opioids. Hydrocodone misuse and abuse contribute to substantial morbidity and mortality, most often in combination with other drugs. IR hydrocodone combination product abuse is primarily oral; however, in some populations, such as those with more advanced substance use disorders, intranasal abuse is fairly common, if not necessarily the preferred or exclusive route. Intranasal drug abuse has been associated with damage to nasal tissues and fungal infections. The available data suggest that injection of hydrocodone combination products is uncommon.

Although the population prevalence of promethazine misuse and abuse is unknown, the data indicate that promethazine misuse and abuse clearly do occur and contribute to morbidity and mortality. Promethazine misuse and abuse appear to occur primarily with combination products containing codeine or dextromethorphan, or in conjunction with other substances, including hydrocodone and other opioids. Anecdotal evidence suggests that some, but not all, individuals who abuse opioids believe promethazine enhances the desirable opioid effects of euphoria as well as the sedation and mitigation of nausea and itching, and some may use it as an opioid-sparing strategy. It is unclear from the available data whether the CNS depressant effects of promethazine contribute in a clinically meaningful additive manner to the risk of opioid overdose and death.

**Conclusions:** Potential harms associated with misuse and abuse should be considered when evaluating the overall risk-benefit balance of Hydexor. Both hydrocodone and promethazine are commonly used in ways not directed by a healthcare provider and contribute to morbidity and mortality in the U.S. Misuse and abuse of promethazine and opioids also clearly occur together, and anecdotal evidence suggests that some, but not all, individuals who abuse opioids believe promethazine enhances opioids' desirable euphoric as well as sedative effects. However, the available epidemiologic data are not informative as to whether Hydexor is more likely to be abused or misused than currently marketed hydrocodone/acetaminophen combination products, or

whether promethazine's CNS depressant effects add meaningfully to the risk of overdose and death associated with opioids when misused or abused concomitantly.

## 1 INTRODUCTION

Hydexor™ is an immediate-release (IR) fixed-dose combination (FDC) drug product containing hydrocodone bitartrate, acetaminophen, and promethazine hydrochloride. Charleston Laboratories (Sponsor) has submitted an NDA (#209257) for Hydexor indicated for the relief of moderate to severe pain while preventing or reducing the opioid induced nausea and vomiting. Although hydrocodone/acetaminophen analgesic products have been marketed for many decades, the addition of promethazine to this drug combination is novel. Hydexor is not formulated with abuse-deterrent properties.

In July 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) issued the report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*.<sup>1</sup> One of the aims of this report was to advise FDA regarding actions it could undertake to balance the needs of pain patients and the need to address opioid misuse. Specifically, the NASEM committee's charge was to help FDA develop a framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse. The report suggests that such a comprehensive approach might involve assessing evidence of a product's potential for diversion and misuse, predicted risks to family members and society, and the likelihood of promoting transition to illicit drugs such as heroin and illicitly manufactured fentanyl. The authors emphasize that use of this broader perspective is both legally permissible under the current statutes and rules and consistent with the public health mission of FDA.<sup>2</sup>

**The purpose of this review is to provide information to inform FDA's and the AADPAC and DSARM joint advisory committee's evaluation of the risk-benefit balance of Hydexor for patients when used as directed, as well as considering potential harms to patients or others arising from misuse and abuse. In particular, this review presents epidemiologic data on the misuse and abuse of hydrocodone (primarily IR hydrocodone/acetaminophen combination products) and promethazine, and associated morbidity and mortality.**

### 1.1 REGULATORY HISTORY

IR hydrocodone/acetaminophen combination products (e.g., Vicodin, Lortab) have been marketed and widely used as analgesics in the U.S. for decades. Upon enactment of the Controlled Substances Act (CSA) in 1971, hydrocodone combination products were listed as Schedule III products; however, in August 2014, the Drug Enforcement Administration (DEA) rescheduled hydrocodone combination products from Schedule III to the more highly controlled Schedule II of the CSA. The new regulation went into effect on October 6, 2014.

Promethazine (e.g., Phenergan) is a phenothiazine derivative introduced in the U.S. in 1946. Since then, it has been widely used in inpatient, perioperative, and outpatient settings for its antiemetic, sedative, and antihistaminic properties. Promethazine is marketed as a single-ingredient product (oral, rectal, and injection forms), and as a FDC with codeine, dextromethorphan, and/or phenylephrine. Promethazine is not scheduled under the CSA.

### 1.2 PRODUCT LABELING

In 2016, FDA required all opioid analgesic products to add the following statements to the **boxed warning** in the drug label:

- *Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.*

- Reserve concomitant prescribing of [opioid product] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation.

Promethazine product labels contain the following warnings:

- **Boxed warning:** *Phenergan (promethazine HCL) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression...caution should be exercised when administering Phenergan to pediatric patients 2 years of age and older...*
- **CNS Depression:** *Phenergan tablets and suppositories may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore such agents should either be eliminated or given in reduced dosage in the presence of promethazine HCL.*
- **Respiratory Depression:** *Phenergan tablets and suppositories may lead to potentially fatal respiratory depression. Use of Phenergan tablets and suppositories in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.*
- **Lower Seizure Threshold:** *Phenergan tablets and suppositories may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.*
- **Severe Tissue Injury, Including Gangrene (Promethazine HCL Injection only):** *Phenergan Injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required.*

## 2 REVIEW METHODS AND MATERIALS

We explored multiple sources of information to help characterize the misuse, abuse, and related adverse outcomes associated with hydrocodone (particularly IR hydrocodone/acetaminophen combination analgesic products), promethazine, as well as the concomitant misuse and abuse of these products. These data sources and the methods used to review and analyze them are described below.

The definitions of misuse and abuse vary according to the source of data, and the terminology used in each data source will be defined. Unless otherwise specified in relation to a specific data source, we will use the following definitions of misuse and abuse, consistent other FDA communications<sup>a</sup>:

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<sup>a</sup> Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER).

*Abuse*: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.

*Misuse*: the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.

## 2.1 REVIEW OF PUBLISHED LITERATURE

Between December 1, 2017 and December 13, 2017, we searched the PubMed database for epidemiologic studies describing misuse or abuse of promethazine, either alone or in combination with opioids, and associated adverse outcomes, using a variety of search term combinations: “promethazine AND abuse,” “promethazine AND misuse,” “promethazine AND opioid,” “promethazine AND respiratory depression,” “promethazine AND potentiate AND opioid.” Studies were limited to English language and human subject studies, and all years were included. Publication titles were screened and abstracts manually reviewed to identify epidemiologic studies relevant to this review. This review also includes information from several hydrocodone abuse studies previously reviewed by FDA that were determined to be relevant. A summary table of the ten published epidemiologic studies that were reviewed fully is included in **Appendix A**.

## 2.2 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS (AAPCC), NATIONAL POISON DATA SYSTEM (NPDS)

The AAPCC maintains the NPDS, which captures data on calls to U.S. poison control centers (PCCs) on a near real-time basis. Currently, AAPCC’s 55 PCCs serve the entire U.S. population, including all 50 states and U.S. territories. PCCs receive calls for exposures to a variety of substances through the Poison Help Line 24 hours per day, offer medical advice, and document reported events in the database. Case records in the database reflect information provided when the public or healthcare professionals call and report an actual or potential exposure to a substance or request information or educational materials. Exposures do not necessarily represent a poisoning or overdose, and the AAPCC does not completely verify the accuracy of every report made to member centers.<sup>3</sup>

Generic codes and product codes for pharmaceutical preparations involving hydrocodone paracetamol (or acetaminophen; APAP) products, excluding cough and cold medications, as well as promethazine were identified using Micromedex® Solutions.<sup>b</sup> Intentional human exposure call data to AAPCC involving hydrocodone/acetaminophen and promethazine among individuals 12 years of age or older during the periods of January 1, 2010 through December 31, 2016 were extracted in December 2017.

For this review, we examined intentional exposure calls (including abuse, misuse, suspected suicide, or unknown intentional exposures; definitions provided in **Appendix B**) for hydrocodone/acetaminophen and promethazine among individuals 12 years of age or older and examined trends and patterns of intentional exposure calls in this group.

Among intentional exposures, we analyzed hydrocodone/acetaminophen and promethazine exposure calls separately for single-substance exposures (i.e., involving only one product) and for total exposures (i.e., involving a single product or multiple products). Analysis of intentional

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April 2015. Accessed November 9, 2017 at

<https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>

<sup>b</sup> Micromedex® Solutions Tox & Drug Product Lookup. 2017 Truven Health Analytics LLC.

<http://www.micromedexsolutions.com/micromedex2/librarian>



exposure calls involving both hydrocodone/acetaminophen and promethazine products together were also conducted. We stratified trends and patterns of intentional exposures calls by reason for exposure (abuse, misuse, suspected suicide, and unknown intentional), route of exposure (ingestion, inhalation, injection, or other) and by selected age groups (12-17, 18-24, 25-44, 45-64, and 65+ years). For promethazine exposure analyses, we also stratified single-substance exposures by single-ingredient products, combination products containing codeine, and other combination products. Using age-specific population estimates prepared by the Census Bureau in collaboration with the National Center for Health Statistics,<sup>c</sup> we calculated age-specific intentional abuse and misuse rates per million population.

We examined medical outcome for single-substance exposures using the following categories: (1) no effect, (2) minor effect, (3) moderate effect, (4) major effect, (5) death or death indirect report. Medical outcomes classified as minor, moderate, major, or death (direct or indirect report) were included if a related clinical effect was documented. Definitions for medical outcome categories can be found in **Appendix B**.

All analyses included an independent quality assurance (QA)/quality control (QC) that was performed using the same criteria by a separate analyst. Results from the two independent analyses agreed.

### **2.3 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM -- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)**

Cases and national estimates of the number of emergency department (ED) visits for drug-related adverse events were based on data from the NEISS-CADES project, a national stratified probability sample of approximately 60 hospitals with a minimum of six beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention (CDC), the US Consumer Product Safety Commission, and the US Food and Drug Administration.<sup>4,5,6,7</sup> In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events, to report up to four medications implicated in each adverse event, and to record narrative descriptions of the incident. Each NEISS-CADES case is assigned a sample weight on the basis of the inverse probability of selection, adjusted for nonresponse and post-stratified to adjust for the number of annual hospital ED visits.

NEISS-CADES has historically focused exclusively on ED visits due to use of medications for a therapeutic indication, or unintended medication exposures by young children. However, in response to a request from FDA, in 2016 NEISS-CADES surveillance activities were expanded to represent the full spectrum of pharmaceutical-related harm, encompassing ED visits resulting from abuse, self-harm, drugs used for unknown intent, and assault, in addition to therapeutic adverse drug events.

Analyses of 2016 NEISS-CADES data were conducted and provided to FDA by the CDC Division of Healthcare Quality Promotion. Complete results and case definitions are included in **Appendix D**. The following query parameters were used to identify cases of interest:

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<sup>c</sup> CDC WONDER. Bridged-Race Population Estimates 1990-2015 Request. Available at: <https://wonder.cdc.gov/Bridged-Race-v2016.HTML>

**Hydrocodone-containing Product Implicated:** Identified by searching for cases with the text string “HYDROCODONE” in any of the generic fields (generic1-4).

**Promethazine-containing Product Implicated:** Identified by searching for cases with the text string “PROMETHAZINE” in any of the generic fields (generic1-4).

**Opioid and Non-selective Antihistamine Both Implicated:** Identified by searching for cases that involved both an opioid-containing product (drugcategory1-4 = “ANALGESICS,OPIOIDS/RELATED”, “ANALGESICS,OPIOIDS/RELATED,POTENTIAL PHARMACEUTICALS”, “ COUGH COLD REMEDIES,NARCOTIC”, “COUGH COLD REMEDIES,NARCOTIC COMBINATIONS”, or “COUGH COLD REMEDIES,NARCOTIC ANTITUSSIVES/EXPECTORANTS”) and a non-selective antihistamine-containing product (generic1-4 contains the text string “ASTEMIZOLE”, “AZATADINE”, “BROMPHENIRAMINE”, “CARBINOXAMINE”, “CHLORPHENIRAMINE”, “CLEMASTINE”, “CYPROHEPTADINE”, “DIMENHYDRINATE”, “DIPHENHYDRAMINE”, “DOXYLAMINE”, “HYDROXYZINE”, “METHDILAZINE”, “PHENINDAMINE”, “PHENIRAMINE/PHENYLTOLOXAMINE/PYRILAMINE”, “PROMETHAZINE”, “TERFENADINE”, “TRIMEPRAZINE”, or “TRIPROLIDINE”).

National estimates of ED visits were calculated by using the SURVEYMEANS procedure in SAS version 9.3 (SAS Institute, Inc, Cary, NC) to account for weighting and complex sample design. NEISS-CADES estimates based on <20 cases or total estimates <1200 for the study period are considered statistically unreliable and are not shown. Similarly, estimates with a coefficient of variation >30% may be statistically unreliable and are noted.

#### **2.4 NATIONAL SURVEY OF DRUG USE AND HEALTH (NSDUH)**

Maintained by the Substance Abuse and Mental Health Services Administration (SAMHSA), NSDUH is an annual, nationally representative survey of the civilian, non-institutionalized, general population in the U.S., with approximately 70,000 randomly selected individuals aged 12 and older surveyed each year. It collects data through face-to-face interviews with a representative sample of the population from residents of households and non-institutional group quarters (e.g., shelters, rooming houses, dormitories) and from civilians living on military bases. The survey excludes homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails and hospitals. NSDUH provides national estimates on respondents’ self-reported drug taking behaviors. For the 2015 survey, a major questionnaire redesign included more detailed questions on past-year use and misuse of specific prescription drugs and the reasons for misuse. For this review, we included relevant information on hydrocodone misuse from detailed NSDUH data tables for survey years 2015 and 2016, published online by SAMHSA.<sup>8,9</sup> NSDUH does not include information on misuse of promethazine.

#### **2.5 NATIONAL VITAL STATISTICS SYSTEM – MORTALITY (NVSS-M) AND DRUG-INVOLVED MORTALITY (DIM) LINKED DATA**

National data on drug-involved mortality were made available to FDA by the National Center for Health Statistics. Drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality (NVSS-M) and Drug-Involved Mortality (DIM) files, with information extracted from the death certificate literal text (see **Appendix C** for further description of this data source).<sup>10</sup>

In NVSS-M, cause of death is captured by ICD-10 codes, where no information on specific drug involvement is available. Our review of DIM data included all deaths of U.S. residents between

January 1, 2010 and December 31, 2015 where hydrocodone and/or promethazine was identified in the literal text as contributing to the death. Cases of misuse/abuse were identified by contextual phrases flagged in the death certificate literal text.

## **2.6 RESEARCHED ABUSE, DIVERSION, AND ADDICTION-RELATED SURVEILLANCE (RADARS®) SYSTEM TREATMENT CENTER PROGRAM (TCP)**

The RADARS® TCP consists of two complementary data sources, the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP) Program. These two programs use the same data collection methods and inclusion criteria, providing data from patients entering treatment for substance use disorders and who report abusing heroin or prescription opioids in the last 30 days. Research participants voluntarily complete a self-administered, anonymous questionnaire within one week of entering the treatment program. The OTP includes a convenience sample of primarily publicly-funded, medication-assisted maintenance treatment programs in urban and rural areas throughout the US. In 2016, 65 treatment centers from 31 states provided information. The SKIP program includes a convenience sample of primarily privately-funded treatment centers, most of which do not use medication-assisted treatment. In 2016, 129 treatment centers from 45 states provided information. While the system captures information from programs across the U.S., the results cannot be considered nationally representative.

Quarterly abuse estimates for 2016 were obtained from RADARS® TCP using reports provided to FDA every six months through an ongoing contract with the Rocky Mountain Poison and Drug Center (RMPDC). The drugs examined in the report included buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, and tramadol, heroin, and loperamide. Abuse prevalence rates were calculated by RMPDC using the quarterly number of abuse mentions for a drug (“use of drug to get high in the past 30 days”) divided by either (1) the number of respondents completing surveys or (2) the number of dosage units (i.e., tablets, capsules) dispensed in the study coverage area (obtained by RMPDC from IMS Health).

## **2.7 INTERNET DRUG DISCUSSION FORUM POSTINGS**

On December 12, 2017, Google was used to search for internet drug discussion forums posts related to abuse of promethazine in combination with opioids, using the following queries: “Does promethazine increase the high from opioids?” and “Does promethazine increase the effects of opioids?” Search results were reviewed to identify links to drug abuse forum discussion threads that appeared topically relevant, and then posts within these discussion threads were manually reviewed to identify those discussing use of promethazine in the setting of opioid abuse. General discussion of themes and examples of posts are presented in this review. This exercise was conducted to gather anecdotal, qualitative information related to the topic of concomitant misuse/abuse of promethazine with opioids, to aid the interpretation of population data. No quantitative or statistical analyses were performed.

## **3 REVIEW RESULTS**

### **3.1 HYDROCODONE MISUSE, ABUSE, AND RELATED ADVERSE OUTCOMES**

#### **National population survey data**

**Table 1** displays the estimated number (in thousands) and percent of respondents reporting any use of prescription pain relief products and hydrocodone products, by age, for 2015 and 2016, in NSDUH. The number and percent of respondents indicating that they misused these products is also displayed. In this survey, *misuse* is defined as “use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.” Due to changes in survey methodology, these values cannot be trended from earlier years.

In 2016, approximately 91.9 million individuals in the U.S. aged 12 years and older are estimated to have used prescription pain relievers, a decrease from approximately 97.5 million in 2015. The estimated number that used hydrocodone products also decreased, from approximately 58.3 million in 2015 to 54.8 million in 2016. The percentage of individuals using hydrocodone products increased with increasing age. In 2016, 11.5 million individuals are estimated to have misused a prescription pain reliever in the past year, and approximately 6.9 million to have misused a hydrocodone product in the past year. Among past-year hydrocodone users in 2016, 12.6% reported misusing the products, although this percentage was higher in the 12-17 and 18-25 year age groups (18.6% and 26.2%, respectively).

**Table 1: Estimated count (in thousands) and percent of past year use and misuse of prescription pain relievers and hydrocodone products, by age, NSDUH 2015-2016.**

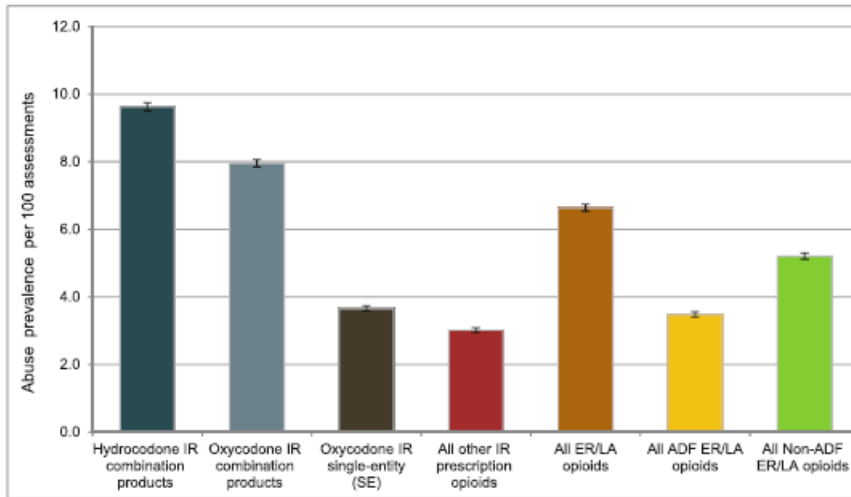
	Age (in years)	2015		2016	
		Any Pain Reliever	Hydrocodone Products	Any Pain Reliever	Hydrocodone Products
<b>Past Year Use, N (%)</b>	12 or older	97,499 (36.4)	58,261 (21.8)	91,846 (34.1)	54,807 (20.3)
	12 to 17	5,650 (22.7)	1,471 (5.9)	4,732 (19.0)	1,240 (5.0)
	18 to 25	12,148 (34.8)	6,906 (19.8)	10,407 (30.1)	5,923 (17.1)
	26 or older	79,701 (38.3)	49,884 (24.0)	76,706 (36.5)	47,644 (22.7)
<b>Past Year Misuse, N (%)</b>	12 or older	12,462 (4.7)	7,193 (2.7)	11,517 (4.3)	6,924 (2.6)
	12 to 17	969 (3.9)	371 (1.5)	881 (3.5)	349 (1.4)
	18 to 25	2,979 (8.5)	1,888 (5.4)	2,454 (7.1)	1,552 (4.5)
	26 or older	8,513 (4.1)	4,934 (2.4)	8,181 (3.9)	5,023 (2.4)
<b>Past Year Misuse Among Past-year Users, %</b>	12 or older	12.8	12.3	12.5	12.6
	12 to 17	17.2	25.2	18.6	18.6
	18 to 25	24.5	27.3	23.6	26.2
	26 or older	10.7	9.9	10.7	10.5

Table generated by reviewer using SAMHSA, Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD; Tables 1.97A-B, 1.98A-B, 1.100A-B, 1.101A-B.-B

**Surveys of individuals entering or being assessed for treatment**

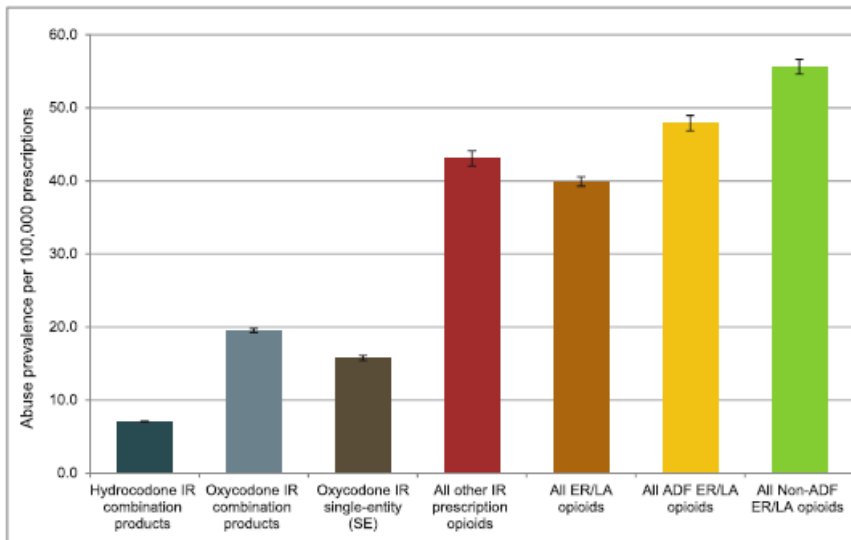
In a study of individuals entering or being assessed for substance use disorder treatment at sites participating in the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) Addiction Severity Index—Multimedia Version (ASI-MV®) surveillance network in the U.S. from 2012-2015, Cassidy et al. found that IR hydrocodone combination products were the most commonly reported drugs abused in the past 30 days (**Figure 1**).<sup>11</sup> However, after adjusting for the number of prescriptions dispensed in the study coverage area, hydrocodone’s abuse rates were the lowest of the opioid categories examined (**Figure 2**). Additional study details can be found in **Appendix A**.

**Figure 1. Prevalence of past 30-day abuse per 100 assessments and 95% CIs among adults assessed for substance abuse treatment in the NAVIPPRO® ASI-MV® system, 1/1/2012-6/30/2015.**



Source: Cassidy et al., 2017

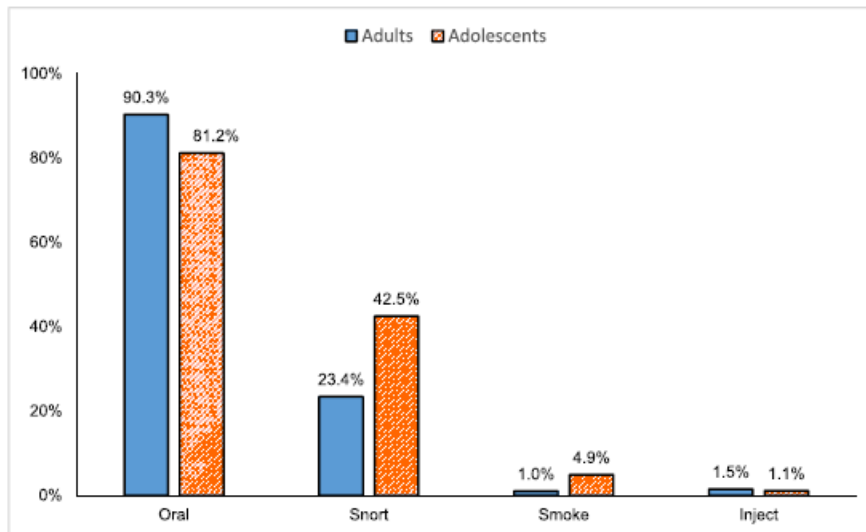
**Figure 2. Prevalence of past 30-day abuse per 100,000 prescriptions dispensed and 95% CIs among adults assessed for substance abuse treatment in the NAVIPPRO® ASI-MV® system, 1/1/2012-6/30/2015.**



Source: Cassidy et al., 2017

In this same study, Cassidy et al. also found that 23% of adults and 42% of adolescents who reported past 30-day abuse of IR hydrocodone combination products indicated that they had snorted the products (**Figure 3**).<sup>11</sup> Only 1.5% of adults and 1.1% of adolescents reported injecting IR hydrocodone combination products.

**Figure 3. Route of administration among past 30-day abusers of hydrocodone immediate-release combination products among adults and adolescents entering or being assessed for substance abuse treatment in the NAVIPPRO® ASI-MV® system, 1/1/2012-6/30/2015**



Source: Cassidy et al., 2017

In the RADARS TCP in 2016, 30% of respondents entering treatment for opioid use disorders indicated abusing hydrocodone in the past 30 days. Only oxycodone (35%) and heroin (57%) had higher abuse prevalence during this time. When adjusted for the number of dosage units (e.g., tablets, capsules) dispensed in the study coverage area, the abuse rate for hydrocodone was the second lowest of all the opioids examined, at 0.083 per 100,000 dosage units dispensed. The lowest, tramadol, had a rate of 0.032 per 100,000 dosage units.

### **Poison Control Center calls**

A total of 102,732 intentional hydrocodone/acetaminophen exposure calls were received by U.S. PCCs from 2010-2016, 31.2% of which were single-substance (i.e., single-product) exposures (**Table 2**). The majority of intentional hydrocodone/acetaminophen exposure calls were categorized as suspected suicides, followed by misuse and abuse. Ingestion was the route of exposure in almost all single-substance intentional hydrocodone/acetaminophen exposures calls, with other routes of exposure, such as inhalation or injection, representing fewer than 1% of single-substance intentional exposure calls.

**Table 2. Total and single-substance intentional hydrocodone/acetaminophen exposures, by exposure reason and route, among individuals 12+ years of age, National Poison Data System 2010-2016**

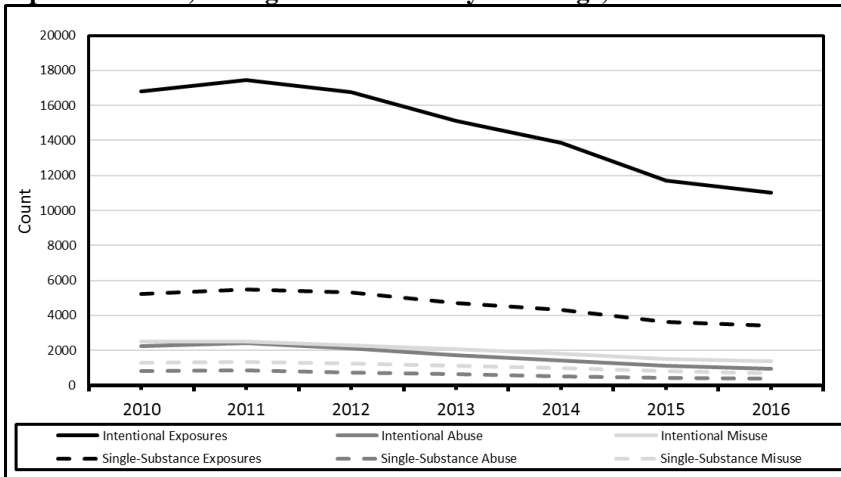
	Total Exposures		Single-Substance	
	N	%	N	%
<b>Exposure Reason</b>				
Intentional Exposures	102,732		32,043	(31.2%)*
Abuse	11,957	11.6%	4,363	13.3%
Misuse	14,058	13.7%	7,502	23.0%
Suspected Suicides	70,822	68.9%	18,075	57.2%
Unknown	5,895	5.7%	2,103	6.6%
<b>Route of Exposure</b>				
Ingested			31,864	99.4%
Inhaled			101	0.3%
Injected			42	0.1%
Other/Unknown			36	0.1%

\* Percent from total exposures

Source: Table generated by reviewer

In general, trends for total hydrocodone/acetaminophen intentional exposure calls declined, from 16,810 calls in 2010 to 11,002 calls in 2016 (**Figure 4**). Declines were also seen for intentional exposure calls indicating abuse or misuse of hydrocodone/acetaminophen and in hydrocodone/acetaminophen single-substance intentional exposure, abuse, and misuse calls.

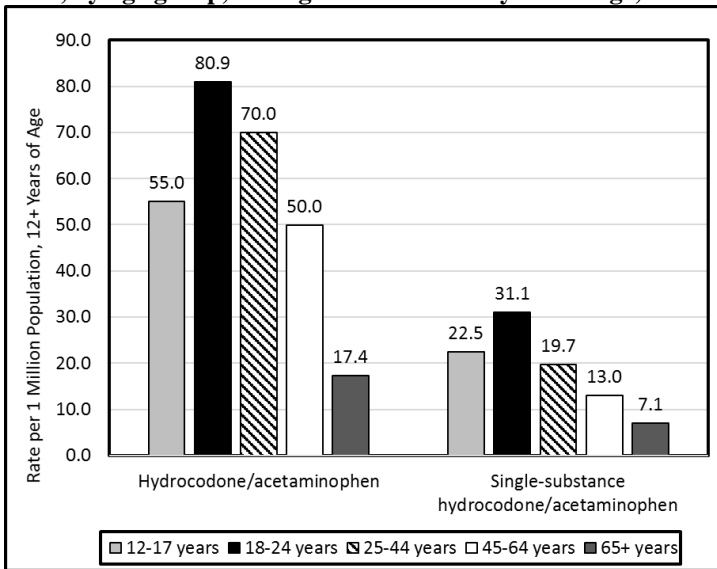
**Figure 4. Trends in total and single-substance intentional hydrocodone/acetaminophen exposures, by exposure reason, among individuals 12+ years of age, National Poison Data System 2010-2016**



Source: Figure generated by reviewer

For both total and single-substance intentional hydrocodone/acetaminophen calls among those ages 12 years and older, the highest rates were in individuals 18-24 years of age (**Figure 5**).

**Figure 5. Total and single-substance intentional hydrocodone/acetaminophen exposure population rates, by age group, among individuals 12+ years of age, National Poison Data System 2010-2016**



Source: Figure generated by reviewer

As shown in **Table 3**, medical outcomes associated with single-substance intentional hydrocodone/acetaminophen calls were most commonly classified as minor effects (38.6%), followed by no effects (32.6%), moderate effects (22.8%), and major effects (5.3%). Less than one percent of intentional single-substance hydrocodone/acetaminophen intentional exposure calls had a medical outcome of death (N=161, 0.8%).

**Table 3. Single-substance intentional hydrocodone/acetaminophen exposures, by exposure reason and medical outcome, among individuals 12+ years of age, National Poison Data System 2010-2016**

Exposure Reason	No Effect		Minor		Moderate		Major		Death	
	N	%	N	%	N	%	N	%	N	%
<b>Hydrocodone/Acetaminophen</b>										
All	6,829	32.6%	8,081	38.6%	4,770	22.8%	1,118	5.3%	161	0.8%
Suicides	4,462	32.4%	5,427	39.4%	3,090	22.5%	696	5.1%	82	0.6%
Abuse	872	33.9%	881	34.3%	621	24.1%	157	6.1%	41	1.6%
Misuse	1,182	34.7%	1,364	40.0%	692	20.3%	156	4.6%	17	0.5%
Unknown	313	25.7%	409	33.6%	367	30.1%	109	8.9%	21	1.7%

Table excludes unrelated effect; the exposure was probably not responsible for the effect(s) and confirmed nonexposures; not followed, judged as nontoxic exposure (clinical effects not expected); Not followed, minimal clinical effects possible (no more than minor effect possible); unable to follow, judged as a potentially toxic exposure; unknown

Source: Table generated by reviewer

### ED visits

Complete results from the analysis of 2016 NEISS-CADES ED visit data are presented in **Appendix D**. In 2016, there were an estimated 5,093 ED visits in the U.S. due to documented abuse of a hydrocodone-containing product, with 2,075 of these visits involving a hydrocodone-containing product without any other implicated pharmaceutical drug products. There were an additional 9,268 visits for self-harm/suicide attempt involving hydrocodone, and 3,365 for therapeutic misuse (e.g., taking a very large amount “to sleep” or taking someone else’s prescription medication). In an additional 8,287 estimated ED visits, a hydrocodone product was implicated, but the intent of drug use was not known (e.g., the patient may have been



unconscious, have had altered mental status, or have been unwilling to describe why the drug was taken).

## **Deaths**

Analysis of the NVSS-M and DIM linked databases found that in the six year period from 2010-2015, there were a total of 20,346 deaths in the U.S. in persons aged 12 years or older where hydrocodone was mentioned on the death certificate as contributing to the death (**Table 4**). Of these, there were 1,593 deaths (7.8%) in which hydrocodone was the only drug mentioned. Of the hydrocodone-involved death cases, 8,012 (39%) specifically mentioned misuse or abuse. Trends for total hydrocodone-involved deaths and for those mentioning misuse/abuse mentions were relatively stable from 2010-2015.

**Table 4. Hydrocodone-involved deaths among individuals 12+ years of age, by year, National Vital Statistics System-M and Drug-Involved Mortality 2010-2015**

<b>Year</b>	<b>Total deaths involving hydrocodone</b>	<b>Hydrocodone only drug mentioned, N (% of total)</b>	<b>Flagged as misuse/abuse, N (% of total)</b>
<b>2010</b>	3,152	232 (7.4)	1,174 (37.2)
<b>2011</b>	3,507	243 (6.9)	1,350 (38.5)
<b>2012</b>	3,346	265 (7.9)	1,297 (38.8)
<b>2013</b>	3,419	298 (8.7)	1,358 (39.7)
<b>2014</b>	3,580	304 (8.5)	1,480 (41.3)
<b>2015</b>	3,342	252 (7.5)	1,353 (40.5)
<b>TOTAL</b>	20,346	1,593 (7.8)	8,012 (39.4)

Source: Table generated by reviewer

## **Additional data on route of abuse of hydrocodone combination products**

In 2016, FDA reviewed and publicly presented data on patterns of hydrocodone combination product abuse, including routes of abuse.<sup>12</sup> This review included data from a variety of sources. One of these was a survey of visitors to a popular online drug discussion forum, [Bluelight.org](http://Bluelight.org). The purpose of this survey was to characterize nonmedical use of hydrocodone combination products. Among survey respondents who reported ever using hydrocodone combination products nonmedically (i.e., other than for medical reasons and as prescribed), almost all (96%) reported having swallowed the pills whole, while 45% reported chewing, 36% drinking in solution, 34% snorting, and 4% reported injecting hydrocodone combination products at some point in their lifetime. When asked to select a single preferred route of administration for hydrocodone combination products, 59% chose swallowing whole, 11% chewing, 10% drinking in solution, 7% snorting, and 2% injecting. Only about 6% of current nonmedical users of hydrocodone combination product reported that their most recent use was via the nasal route. FDA also reviewed additional data from the NAVIPPRO® ASI-MV® survey that showed that, although snorting hydrocodone combination products was fairly common among those entering or being assessed for substance abuse treatment, only about 6-7% reported that snorting was the exclusive route by which they abused hydrocodone combination products. FDA's review found that route of abuse patterns for hydrocodone combination products varied widely across different populations and survey settings. For example, a published survey of 101 rural and 111 urban nonmedical prescription drug users in Kentucky in 2010 found that, in the rural group, 74%

reported snorting hydrocodone at some point in their lifetime, whereas in the urban group, only 6% reporting snorting hydrocodone. No respondents in either group reported injecting hydrocodone. Of note, the rural group had much higher Addiction Severity Scores than those of their urban counterparts, indicating more severe drug problems in general.<sup>13</sup> FDA also reviewed published case series that described nasal tissue damage and fungal infections associated with chronic intranasal abuse of opioids and other drugs, although the actual incidence of these outcomes could not be quantified.<sup>12</sup>

### 3.2 PROMETHAZINE MISUSE, ABUSE, AND RELATED OUTCOMES, ALONE AND IN COMBINATION WITH HYDROCODONE OR OTHER OPIOIDS

#### Poison Control Center calls

From 2010-2016, U.S. PCCs received a total of 15,119 intentional promethazine exposure calls, 4,293 of which were single-substance (i.e., single product) exposures (**Table 5**). Promethazine intentional exposure calls were predominately categorized as suspected suicides, followed by misuse and abuse. Among the 2,967 abuse and misuse calls, approximately half (n=1,425) were single-substance exposures. Among these single-substance promethazine abuse and misuse calls, 683 (48%) involved single-ingredient promethazine products, while 438 (31%) involved promethazine-codeine combination products. A total of 1,300 intentional exposure calls involved both promethazine and hydrocodone/acetaminophen. Approximately 83% of these calls were categorized as suspected suicides and roughly 12% were classified as abuse or misuse. Ingestion was the route reported for nearly all intentional single-substance promethazine exposure calls. Other routes of exposure represented less than 1% of single-substance intentional exposure calls.

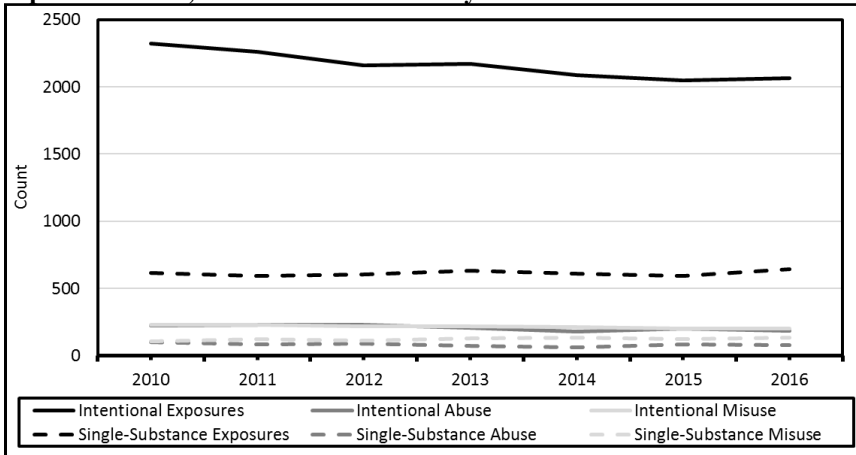
**Table 5. Total and single-substance intentional promethazine exposure calls and intentional exposure calls involving promethazine with hydrocodone/acetaminophen, by exposure reason and route, among individual 12+ years of age, National Poison Data System 2010-2016**

Exposure Reason	Total Exposures		Single-Substance Exposures							
	N	%	Overall		Single-Ingredient		Containing Codeine		Other <sup>#</sup>	
			N	%	N	%	N	%	N	%
<b>Promethazine</b>										
Intentional Exposures	15,119		4,293	(28.4%)*	3,063	(71.3%)^	697	(16.2%)^	533	(14.1%)^
Abuse	1,451	9.6%	570	13.4%	233	7.6%	207	29.7%	130	24.4%
Misuse	1,516	10.0%	855	19.7%	450	14.7%	231	33.1%	174	32.6%
Suspected Suicides	11,240	74.3%	2,517	58.7%	2,138	69.8%	194	27.8%	185	34.7%
Unknown	912	6.0%	351	8.3%	242	7.9%	65	9.3%	44	8.3%
<b>Promethazine &amp; Hydrocodone/Acetaminophen</b>										
Intentional Exposures	1,300									
Abuse	79	6.1%								
Misuse	85	6.5%								
Suspected Suicides	1,076	82.8%								
Unknown	60	4.6%								
<b>Route of Exposure</b>										
<b>Promethazine</b>										
Ingested			4,245	98.9%	3,016	98.5%	697	100%	532	99.8%
Inhaled			10	0.2%	10	0.3%	0	0%	0	0%
Injected			16	0.4%	15	0.5%	0	0%	1	0.2%
Other/Unknown			22	0.5%	22	0.7%	0	0%	0	0%
* Percent from total exposures										
^ Percent from single-substance exposures										
# Includes single-substance promethazine exposure with dextromethorphan, meperidine, pseudoephedrine, and/or ethanol										

Source: Table generated by reviewer

Overall, trends for total intentional promethazine exposure calls declined from 2010 to 2016 (**Figure 6**). The number of intentional abuse and misuse calls involving promethazine remained relatively steady. Relatively stable trends in annual counts were also observed for single-substance intentional, abuse, and misuse promethazine calls.

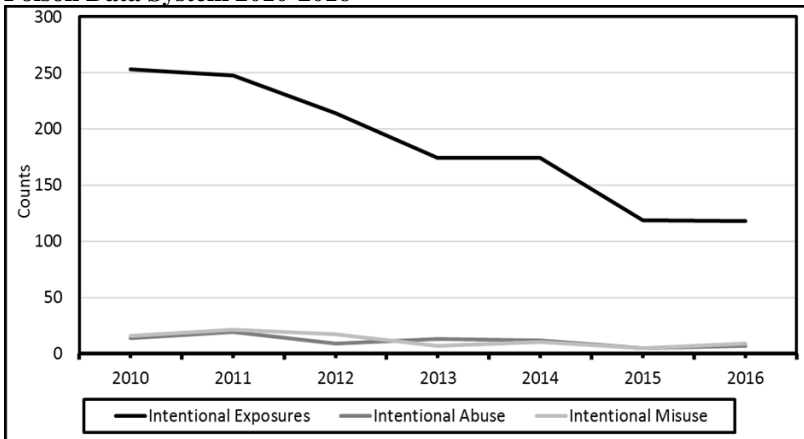
**Figure 6. Trends in intentional promethazine exposure calls among individuals 12+ years of age, by exposure reason, National Poison Data System 2010-2016**



Source: Figure generated by reviewer

From 2010 to 2016, the total number of intentional exposure calls involving both promethazine and hydrocodone/acetaminophen declined. (**Figure 7**). The number of intentional exposure calls indicating abuse or misuse involving both promethazine with hydrocodone/acetaminophen remained relatively low and steady during this period.

**Figure 7. Trends in intentional exposure calls involving both promethazine and hydrocodone/acetaminophen, among individuals 12+ years of age, by exposure reason, National Poison Data System 2010-2016**

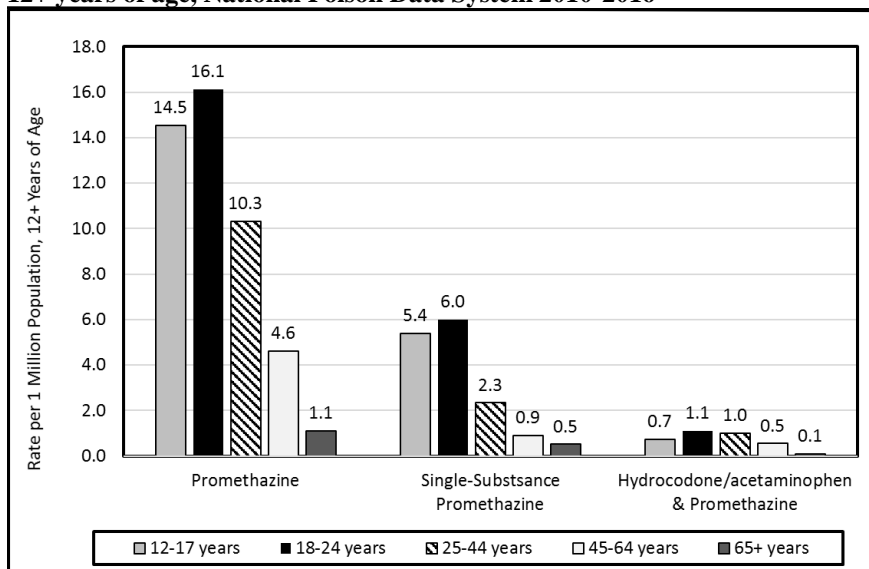


Source: Figure generated by reviewer

For total and single-substance intentional promethazine exposure calls and for calls involving both promethazine and hydrocodone/acetaminophen, individuals 18-24 years had the highest call rate (**Figure 8**).

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**Figure 8. Intentional exposure population call rates for total and single-substance promethazine calls and calls involving promethazine with hydrocodone/acetaminophen, by age group, among individual 12+ years of age, National Poison Data System 2010-2016**



Source: Figure generated by reviewer

Medical outcomes associated with intentional single-substance calls involving promethazine-containing products were predominantly classified as minor effects, followed by moderate effects, no effects, and major effects (**Table 6**). From 2010-2016, there were three single-substance promethazine intentional exposure calls with a medical outcome of death, and of these one involved single-ingredient promethazine.

**Table 6. Medical outcomes associated with single-substance promethazine intentional exposure calls, among individuals 12+ years of age, National Poison Data System 2010-2016**

Exposure	No Effect		Minor		Moderate		Major		Death	
	N	%	N	%	N	%	N	%	N	%
Promethazine	529	17.8%	1255	42.2%	1105	37.1%	85	2.9%	3	0.1%
Single-Ingredient Promethazine	419	18.7%	918	40.9%	845	37.6%	62	2.8%	1	0.0%
Promethazine Containing Codeine	73	18.8%	176	45.4%	125	32.2%	12	3.1%	2	0.5%

Table excludes unrelated effect; the exposure was probably not responsible for the effect(s) and confirmed nonexposures; not followed, judged as nontoxic exposure (clinical effects not expected); Not followed, minimal clinical effects possible (no more than minor effect possible); unable to follow, judged as a potentially toxic exposure; unknown.

Source: Figure generated by reviewer

### **ED visits**

Complete results of the 2016 NEISS-CADES ED visit analysis are presented in **Appendix D**. Within the 2016 NEISS-CADES sample, there were 18 cases where the ED visit was due to abuse of a promethazine-containing product, with an additional 13 cases of self-harm/suicide attempt, one case of therapeutic misuse, and eight cases in which intent of drug use was not known. Case numbers were not large enough to generate reliable national estimates for individual case types, but combined, there were 40 cases and an estimated 2,883 ED visits nationally for abuse, self-harm/suicide attempt, therapeutic misuse, or unknown intent involving a

promethazine-containing product. Combined, from the same hospitals, there were only 9 cases of abuse, therapeutic misuse, self-harm/suicide attempt or unknown intent where a promethazine-containing product *alone* was implicated. Reliable national estimates could not be generated for these cases.

In 2016, there were 20 cases corresponding to an estimated 1,362 ED visits due to abuse of a non-selective antihistamine in combination with a prescription opioid. An additional 30 cases of self-harm attempts, 3 cases of therapeutic misuse, and 17 cases in which the intent was not clearly documented were attributed to a non-selective antihistamine in combination with a prescription opioid.

### **Deaths**

Analysis of the NVSS-M and DIM linked databases found that, from 2010-2015, there were 1,696 deaths in the U.S. in persons aged 12 years or older where promethazine was mentioned on the death certificate as contributing to the death (**Table 7**). In 24 of these, promethazine was the only drug mentioned. Trends were relatively stable for promethazine-involved deaths. Thirty-five percent of promethazine-involved deaths were specifically flagged as involving misuse or abuse.

**Table 7. Promethazine-involved deaths among individuals 12+ years of age, by year, National Vital Statistics System-M and Drug-Involved Mortality 2010-2015**

<b>Year</b>	<b>Total deaths involving promethazine</b>	<b>Promethazine only drug mentioned, N (% of total)</b>	<b>Flagged as misuse/abuse, N (% of total)</b>
<b>2010</b>	283	4 (1.4)	95 (33.6)
<b>2011</b>	274	5 (1.8)	89 (32.5)
<b>2012</b>	275	3 (1.1)	90 (32.7)
<b>2013</b>	254	2 (0.8)	94 (37.0)
<b>2014</b>	310	3 (1.0)	114 (36.8)
<b>2015</b>	300	7 (2.3)	104 (34.7)
<b>TOTAL</b>	1,696	24 (1.4)	586 (34.6)

Source: Table generated by reviewer

### **Published literature**

Abuse of promethazine in combination with an opioid has been described in the literature, primarily in relation to the abuse of cough syrups containing promethazine and codeine. Known by various names such as “purple drank,” “lean,” and “sizzurp,” abuse of cocktails containing codeine-promethazine cough syrup was popularized in the 1990s by a number of rap artists, primarily in the Houston, Texas area.<sup>14,15</sup> A 2003 study of predominantly African American middle and high school students in Houston found that 55% of students interviewed reported abusing codeine-promethazine cough syrup.<sup>15</sup> In a separate study, college students who abused codeine-promethazine cough syrup described strong sedative and euphoric effects, as well as addiction and withdrawal symptoms when use is discontinued.<sup>16</sup> A more recent survey at a large southeastern university in 2011 found lower prevalence rates, with approximately 4% of females and 9% of males reporting abuse of codeine-promethazine cough syrup. In this study, use in whites was similar to use in African Americans.<sup>14</sup>

One study of injection heroin users in Vietnam found a high prevalence (75%) of promethazine use in conjunction with injection of heroin. Injectors described using promethazine to augment a suboptimal dose of heroin, or pre-dosing in anticipation of impending withdrawal. However, most users stated that they disliked the actual effects of promethazine, including occasional hallucinogenic properties.<sup>17</sup> Two studies describe use and misuse of promethazine in several opioid user groups in San Francisco: patients with chronic pain receiving opioids, patients with opioid use disorders in methadone maintenance programs, and community-based injection heroin users. In the chronic pain group, 9% had urine tests that were positive for promethazine, while only half of these had an active prescription for promethazine.<sup>18</sup> Promethazine positivity was associated with having a urine that was positive for benzodiazepines without having a benzodiazepine prescription. However, having a prescription only for hydrocodone was negatively associated with having a promethazine-positive urine. In the methadone maintenance group, 26% of urine tests were positive for promethazine, and of these only 15% had an active prescription for promethazine. Among community-based injection heroin users, 17% reported recent promethazine use, the majority of which was without an active prescription for the drug.<sup>19</sup> When interviewed, both current injection heroin users and methadone maintenance patients reported use of promethazine without a prescription. Study authors also noted, from their own clinical practice, anecdotal reports of promethazine use by methadone maintenance patients to potentiate the “high” from methadone.

### **Internet discussion forum posts**

The internet drug abuse discussion forums Bluelight.org and Drugs-forum.com both contained discussion threads about the use of promethazine in conjunction with opioid abuse. Opinions were mixed regarding whether promethazine enhances the opioid abuse experience, with some discussants stating that promethazine potentiates the euphoria from opioids, and others stating that promethazine adds to the sedative effects of opioids but not necessarily the euphoria. Some discussants enjoyed this added sedative effect (i.e., the “nod”), while others felt it detracted from the experience. Other posts focused primarily on promethazine’s anti-emetic and anti-itching effects as reasons for using promethazine when abusing opioids. At least one post suggests use of promethazine as an opioid-sparing strategy (“...have a bunch more doses left over...”). Examples of these different types of posts are included verbatim below:

#### **Posts that endorse promethazine as enhancing the euphoric effects of opioids:**

- *...since taking them with my Roxicodones, I will NEVER take [opiates] alone without Promethazine. That's how much of a diff there is. I'm so much more doped out and euphoric, and have a bunch more doses left over for those painful days. Win, win.<sup>20</sup>*
- *Despite what some users report, first-generation antihistamines do not reduce euphoria, they enhance it as well as increase those effects already produced by the opiates, making them a great addition to any opiate user's arsenal.<sup>21</sup>*
- *I have used promethazine a few times with codeine. He always took a couple of prometh' pills just after the peak of the codeine high ... so any where between 1 hour and 2 hours after ingestion. If You took some after that it creates almost a 2nd high but a little different.<sup>22</sup>*
- *Taking 1 pill of any of the following med 30 mins before an Opiate will make the high stronger:  
-Dramamine (this is dimenhydrinate, and it is used for motion-sickness)*

- Benadryl (this is diphenhydramine, and it is used against allergies)
- OTC sleeping pills that contains either Promethazine or Doxylamine (I don't know the brand names)<sup>23</sup>

Posts that do not endorse promethazine as enhancing euphoria from opioids but describe “potentiation” of opioids, increased sedation, or other desirable effects when abused in combination with opioids:

- *Promethazine is generally regarded as potentiating all opiates by making the nod more intense. If you like your high to be really mellow, sink into the bed, sleep for a day kind of experience 25mg promethazine before and another 25mg during will go down nicely. Works good with codeine too 😊<sup>24</sup>*
- *[Promethazine's] very sedating because of antihistaminergic and dopamine blocking effects...so it'll potentiate sedating effects from Vicodin, but not the euphoric properties.<sup>24</sup>*
- *Promethazine (aka "phenergan") is RX only, anti nausea & certainly potentiates opiates.<sup>20</sup>*
- *I think promethazine is quite possibly one of the greatest medications ever. It does potentiate and also takes away the yuckies.<sup>24</sup>*
- *Down a glass of grapefruit juice and pop the hydrocodone & promethazine. While the promethazine won't really potentiate your hydro (unless you take a lot & mostly it will increase the sedative effects), it is good for keeping the itchiness away.<sup>25</sup>*
- *yes promethazine potentiates opiates to the extent that it mainly adds to the sedation/nodding... but don't take too much promethazine as it can render u delirious in high doses (IME upwards of 300mg)...  
i used to potentiate my morphine with 100mg promethazine, 400mg hydroxyzine and some benzos... made for a good noddddd... ahh those were the days...<sup>24</sup>*

Posts that describe undesirable effects of promethazine when abused in combination with opioids:

- *Do not bother with the promethazine. It just makes you more sedated and I find it "clouds" my opiate high/euphoria.<sup>25</sup>*
- *...I'm not a big fan of mixing in the promethazine. Grapefruit juice is much better. I hate anything that like you said "clouds" my high/euphoria sensation.<sup>25</sup>*
- *I would suspect that the promethazine would potentiate the sedating effects of the hydrocodone but likely not the euphoric effects. From my own personal experience potentiation of opiates with non-opioids comes at the cost of "dirtying" the high. The high may become more intense but less euphoric. The euphoria in my opinion is what, above all else, makes opiates so enjoyable.<sup>26</sup>*
- *...If you want to potentiate your roxy[codone], [promethazine, diphenhydramine, and hydroxyzine] will indeed help with that, but you might be too asleep to enjoy it...<sup>20</sup>*



- *...many believe that antihistamines like diphenhydramine and promethazine are useful "potentators" [sic] for opiates. That was all good, until I continued researching and found that some people claim that these antihistamines reduce the euphoria that opiates induce.<sup>21</sup>*

## 4 DISCUSSION

### 4.1 SUMMARY OF THE DATA

In evaluating a new opioid product for approval, FDA must consider the risks and benefits to patients when the drug is used as directed, as well as potential harms to the patient or public arising from misuse and abuse. Although no epidemiologic data will be available for a particular product until after it is marketed, postmarketing data on similar products or drug components of a combination product may be informative when anticipating how the new product might be misused and to what extent this might result in adverse outcomes. The available data indicate that currently marketed hydrocodone products—predominantly immediate-release hydrocodone/acetaminophen combination products—are widely used, misused, and abused in the U.S., and that hydrocodone combination products contribute to substantial morbidity and mortality. In 2016, almost 7 million individuals were estimated to have misused or abused hydrocodone in the past year, representing about 13% of the total number who reported using the products. Abuse of hydrocodone combination products is also highly prevalent among individuals entering or being assessed for substance use disorder treatment; however, relative to total number of prescriptions dispensed, abuse rates for these drugs are lower than for most other opioid analgesics. In 2016, documented misuse and abuse of hydrocodone-containing products is estimated to have contributed to more than 8,000 ED visits and in additional estimated 8,000 ED visits, a hydrocodone product was implicated, but the intent of drug use was not clearly documented. From 2010-2016, there were approximately 26,000 calls to U.S. PCCs involving misuse or abuse of hydrocodone/acetaminophen products, and from 2010 to 2015, 20,346 death certificates in the U.S. listed hydrocodone as a drug contributing to the death. In the large majority of deaths involving hydrocodone, additional substances were implicated in the death. Previous published analyses of death certificate data indicate that the most frequent concomitantly implicated drugs were benzodiazepines and other opioids.<sup>27</sup>

Abuse and misuse of hydrocodone combination products primarily occurs through the oral route. In some populations—particularly those enriched with individuals with more advanced substance use disorders—intranasal abuse is relatively common as well, although very little intranasal exposure was reported for single-substance intentional exposure calls to poison centers. In an internet-based survey of people visiting a drug abuse discussion forum, only a small proportion identified snorting as if usually not the preferred or exclusive route for abuse of these products. Case series have described serious nasal tissue damage and fungal infections due to chronic intranasal drug abuse; however, the risk of these adverse effects has not been quantified.

Population survey data on promethazine misuse and abuse are not available, and therefore the prevalence of this behavior in the U.S. is unknown. Nonetheless, the available data indicate that abuse and misuse of promethazine occur in non-trivial numbers, although predominantly with combination products that include other ingredients such as codeine or dextromethorphan, or concomitantly with additional substances. It is estimated that there were 2,883 ED visits for abuse, self-harm/suicide attempt, therapeutic misuse, or unknown intent involving promethazine-containing products in 2016, the large majority involving other drugs in addition to promethazine.

From 2010-2016, there were almost 3,000 intentional abuse or misuse exposure calls to U.S. PCCs involving a promethazine-containing product. Of these, approximately half were single-product exposures, and about half of these were single-ingredient promethazine products. Previously published analyses of U.S. PCC call data indicate that the rate of promethazine misuse and abuse calls approximately doubled over the 11-year period from 2002-2012.<sup>28</sup> Finally, from 2010-2015, there were almost 1,700 deaths documented as involving promethazine, but only 24 in which promethazine was the only drug implicated.

Misuse and abuse of promethazine and other antihistamines clearly occur concomitantly with opioids. In 2016, there were an estimated 1,362 ED visits related to abuse of promethazine or other non-selective anti-histamines in combination with opioids. From 2010-2016, there were 164 intentional abuse or misuse PCC calls involving both promethazine and hydrocodone/acetaminophen specifically. Abuse of “cocktails” containing promethazine-codeine cough syrups has been well documented in some areas and demographic groups in the U.S., although it is not clear whether or how the effects or desirability of these products differ from other opioid products that do not contain promethazine. Several other published studies suggest that nonmedical (non-prescribed) use of promethazine may be fairly common in some opioid user populations, particularly those in methadone maintenance programs or injecting heroin. Internet drug abuse discussion forums and anecdotal information in published studies suggest that some, but not all, individuals believe that promethazine potentiates the euphoric effects or enhances pleasurable sedative effects of opioids (i.e. the “nod”). Others primarily note promethazine’s mitigation of nausea or itching, while some describe the effects of promethazine as undesirable when taken with opioids for the purpose of getting high.

As described in product labeling, promethazine is a CNS depressant. It is therefore included in the broad class of drugs (i.e., CNS depressants) that may increase the risk of overdose and death associated with opioids when used concomitantly, as described in the boxed warning on all opioid analgesic products. However, the epidemiologic data are not informative about whether the CNS depressant effects of promethazine contribute in a clinically meaningful manner to the risk of overdose and death associated with opioids, when misused or abused concomitantly.

## **4.2 LIMITATIONS OF DATA AND REVIEWED STUDIES**

All the studies and data sources reviewed have limitations, and these should be kept in mind when interpreting the data. Key limitations of published studies are noted in the epidemiologic study summary table, **Appendix A**.

### **NPDS**

PCC call data should not be interpreted as representing the complete incidence of national exposures to any substance. These data only capture abuse events if the exposure resulted in a call to a PCC. PCC data rely on information electively shared by patients and healthcare personnel, and most substance classification is based on history alone and does not involve any biologic confirmation. Drug exposures resulting in unattended or out-of-hospital death are unlikely to generate a call to a PCC, and therefore, fatal poisonings are expected to be substantially under-reported in PCC call data.<sup>29</sup> Follow-up and medical outcome are not available for all calls. It is possible that changes in poison center call rates in part reflect changes in public and professional awareness of the risks associated with specific drugs, and awareness of the abuse potential of a drug among call center personnel could also increase the likelihood of an exposure being coded as intentional abuse. Call rates may also be influenced by general changes in use of PCCs over time.<sup>30</sup>

## NEISS-CADES

NEISS-CADES data can be used to calculate national estimates, but NEISS-CADES does not include cases that do not result in an ED visit or that result in death before or during ED evaluation. The quality of these surveillance data depend on the completeness and accuracy of medical record documentation by the healthcare provider and, to be included in the database, cases require documentation by the healthcare provider that a drug or drug class (e.g., “opioid”) was implicated in the ED visit. Up to four medications may be recorded as being implicated in a case, but it is possible that additional drugs were involved and not recorded.

## NSDUH

Although NSDUH is one of the few resources capable of producing national estimates of prescription drug misuse and abuse, it is subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias, and in general it is not sufficiently detailed to examine specific opioid branded products and formulations. NSDUH does not include questions on all drugs with potential for misuse or abuse, and it does not provide any information on promethazine. Information on route of administration is very limited. Individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility.

## NVSS-M and DIM linked data

The DIM dataset relies on drug mentions to identify cases. Hydrocodone- and promethazine-involved deaths can only be identified when these substances are specifically mentioned on death certificates. Therefore, findings may describe the minimum number of hydrocodone- or promethazine-involved deaths. Our estimates for the number of misuse/abuse cases also rely on mentions in the literal text and are also likely under-reported. Moreover, there may have been changes in the probability of reporting or testing for specific drug-involvement in the literal text over the course of the study period.

## RADARS® TCP and NAVIPPRO® ASI-MV® data

An important limitation of data collected from people entering or being assessed for substance use disorder treatment is the potential for misclassification, including in the identification of the specific product(s) being abused. Another limitation is that these are convenience samples, and because they are enriched with individuals with advanced substance use disorders who have sought or been referred for treatment or assessment, patterns observed in these study populations may not reflect those that exist in a broader population of individuals who abuse drugs. Numerous factors—for example, judicial referral policies and availability and funding of substance use disorder treatment—can affect the probability that an individual who is abusing or addicted to prescription opioids is assessed for treatment and included in the sample. Finally, these data are not geographically representative of all individuals being assessed for substance use disorder treatment in the U.S.

## Internet surveys and drug discussion forum postings

Surveys that recruit visitors on drug discussion forums are useful in that these are enriched samples of individuals with drug abuse experience. However, the selection forces operating are not well understood, and it is not known to what degree these survey participants represent abuse patterns and behaviors in the broader population. For example, visitors to these sites may be more, or less, likely to abuse drugs via non-oral routes.

The review of internet drug discussion forum postings should be considered exploratory and qualitative. The search strategy was not systematic or comprehensive, and findings did not

include information from any websites or applications that require registration or proprietary account access, for example social media sites. There is no way to verify information contained in these posts. Individuals may misidentify products, and sometimes report rumors or hearsay rather than personal experiences.

## 5 CONCLUSIONS

Potential harms associated with misuse and abuse should be considered when evaluating the overall risk-benefit balance of Hydexor. Both hydrocodone and promethazine are commonly used in ways not directed by a healthcare provider and contribute to morbidity and mortality in the U.S. Misuse and abuse of promethazine and opioids also clearly occur together, and anecdotal evidence suggests that some, but not all, individuals who abuse opioids believe promethazine enhances opioids' desirable euphoric as well as sedative effects. However, the available epidemiologic data are not informative as to whether Hydexor is more likely to be abused or misused than currently marketed hydrocodone/acetaminophen products, or whether promethazine's CNS depressant effects add meaningfully to the risk of overdose and death associated with opioids when misused or abused concomitantly.

## 6 APPENDICES

### 6.1 APPENDIX A: EPIDEMIOLOGIC STUDY SUMMARY TABLE

Study	Population/setting	Design/Methods	Key Results	Comments/limitations
Agnich, 2013 <sup>14</sup>	Students in 40 randomly selected classes at a large public university in the southeastern U.S., 2011  N=2,349; response rate 80.4%.	Cross-sectional study using print surveys	Lifetime prevalence of promethazine-codeine cough syrup nonmedical use: <ul style="list-style-type: none"> <li>• 9.3% in males</li> <li>• 3.9% in females</li> </ul> Use in whites was similar to that in African Americans, more common among Hispanics and Native Americans.	Suggests nonmedical promethazine-codeine cough syrup use (in lifetime) may be prevalent at relatively low levels in this general university population, but is clearly not limited to the well-described use among African American youth in the Houston area.  Single university, findings may not be generalizable to other university student populations or other demographic groups.
Cassidy, 2017 <sup>11</sup>	Adults entering or being assessed for substance use disorder treatment at U.S. sites within the NAVIPPRO® ASI-MV® surveillance network, 2012-2015  Adolescents 13-18 years old being assessed for substance abuse treatment within the CHAT surveillance network.	Cross-sectional study using computerized assessments	Per 100 assessments, IR hydrocodone combination products had higher abuse prevalence than any other opioid category.  Per 100,000 prescriptions dispensed, the abuse prevalence for hydrocodone combination products was lower than any other opioid category.  23.4% of adults and 42.5% of adolescents reported snorting hydrocodone combination products. 1.5% and 1.1%, respectively, report injecting them.	Suggests that abuse of hydrocodone combination products is highly prevalent in this population, but relative to prescription volume may be less likely to be abused than other opioid analgesic products.  Intranasal, but not injection, abuse of hydrocodone combination products is relatively common in this population.  Enriched sample with high prevalence of advanced substance use disorders, which is associated with more non-oral abuse. Drug abuse patterns in this population may not reflect patterns in a broader population of drug abusers.  Not geographically representative of the U.S.

Study	Population/setting	Design/Methods	Key Results	Comments/limitations
Clatts, 2010 <sup>17</sup>	179 new injection heroin users in Hanoi, Vietnam, 2005-2006.	Cross-sectional mixed-methods study using face-to-face interviews	<p>75% of sample had used promethazine hydrochloride (PHC), and of those, all were currently using it.</p> <p>Most described mixing heroin, PHC, and other drugs (primarily Novocaine) for injection.</p> <p>Injectors described using PHC to augment a suboptimal dose of heroin, or pre-dosing in anticipation of impending withdrawal. Most disliked its effects (including occasional hallucinogenic properties).</p> <p>Most were unaware of risk of vein/tissue damage with injection of PHC.</p>	<p>Product misclassification may have occurred.</p> <p>Convenience sample; non-U.S. study—reported practices may differ from those among injection heroin users the U.S.</p> <p>Little specific information about the intent behind promethazine use, i.e., whether it was being used to potentiate or extend the effects of heroin, how it mitigated withdrawal symptoms, or whether there were any adverse effects associated with promethazine use in this setting.</p>
Lynch, 2015 <sup>18</sup>	921 chronic pain patients receiving opioids in five public health clinics in San Francisco, 2012	Cross sectional study using urine analysis on stored urine samples, in conjunction with medical record review	<p>82 chronic pain patients (9%) had urine positive for promethazine, and only half of these had an active prescription for promethazine.</p> <p>Promethazine positivity was associated with benzodiazepine positivity without a prescription.</p> <p>Having a prescription only for hydrocodone was negatively associated with having a promethazine-positive urine.</p> <p>Being in methadone MAT was strongly associated with promethazine positivity.</p>	<p>Suggests that nonmedical use of promethazine may be prevalent, although at relatively low levels, among patients receiving opioids for chronic pain and may be associated with other higher-risk behaviors such as concomitant benzodiazepine use.</p> <p>No information about intent, reasons for use, or associated adverse effects.</p> <p>Some patients may have received promethazine prescriptions at outside clinics, or have expired prescriptions, which may not have been detected through this medical record review.</p> <p>Unclear if urine testing was done on all patients, or only if clinically indicated (possible detection bias). Unknown sensitivity/specificity of promethazine urine tests using the defined cut-offs.</p>

Study	Population/setting	Design/Methods	Key Results	Comments/limitations
				Convenience sample. Findings may not be broadly generalizable.
Peters, 2003 <sup>15</sup>	<p>87 middle and high school students in Houston, majority were African American.</p> <p>Only 87 out of 587 invited students returned parental consent forms and participated in the survey</p>	Cross-sectional mixed-methods study using semi-structured interviews	<p>Of 87 students interviewed, 48 (55%) reported current codeine/promethazine hydrochloride cough syrup (CPHCS) use.</p> <p>Users described media modeling, peer pressure/cool image, euphoric effect, easy accessibility as reasons for use.</p> <p>Adolescents believe that it takes very little time to develop an addiction to CPHCS—majority responded “first time” or “second time” as number of times it takes for someone to become addicted to CPHCS.</p>	<p>Descriptive study, suggesting high prevalence of promethazine/codeine cough syrup misuse/abuse in this particular population.</p> <p>Convenience sample: findings may not be generalizable to other student populations and geographic areas.</p> <p>Perception that this product is highly addictive, but no way to verify or compare to other opioid-containing products.</p> <p>Low response rate. Possible selection, non-response bias.</p>
Peters, 2007 <sup>16</sup>	307 college students at a historically black southwestern U.S. university	Cross-sectional mixed-methods study using semi-structured interviews	<p>61 out of 307 students (20%) reported current misuse of codeine/promethazine hydrochloride cough syrup (CPHCS).</p> <p>Participants described strong sedative effects, euphoria, addiction, and withdrawal.</p>	<p>Descriptive study, suggesting fairly high prevalence of promethazine/codeine cough syrup misuse/abuse in this particular college population. Findings may not be generalizable to other student populations and geographic areas.</p> <p>Unclear sampling/recruitment strategy—appears to be simple convenience sample.</p>



Study	Population/setting	Design/Methods	Key Results	Comments/limitations
Shapiro, 2013 <sup>19</sup>	<ol style="list-style-type: none"> <li>1. 334 methadone maintenance patients in San Francisco (SF)</li> <li>2. 200 community-based injection drug users (IDUs) in SF, including 139 heroin users; recruited by outreach worker</li> </ol>	<p>Cross-sectional study:</p> <ol style="list-style-type: none"> <li>1. Urine testing on stored urine samples, and review of SF Health Department clinical database used for medication management and prescribing (methadone maintenance population)</li> <li>2. In-person interviews (community-based IDU population)</li> </ol>	<ol style="list-style-type: none"> <li>1. Among methadone maintenance patients, 26% of urines tested positive for promethazine. Of these, only 15% had an open prescription for promethazine.  Benzodiazepine positive urine was significantly associated with promethazine-positive urine.  Study authors note anecdotal reports in their own clinical practice of promethazine use by methadone maintenance patients to potentiate the “high” from methadone.</li> <li>2. Among community-based injection heroin users, 17% reported using promethazine in the past month. Of these, only 17% reported having a current prescription for promethazine.  Promethazine use was strongly associated with reported use of non-prescribed opioid pills.</li> </ol>	<p>Suggests that promethazine is commonly used nonmedically in these populations and may be associated with other risky drug use behaviors (e.g., benzodiazepine use and use of non-prescribed opioid pills).</p> <p>Some methadone patient may have received prescriptions outside of the SF Health Department system, or have expired prescriptions, that may not have been detected in this database.</p> <p>Unclear if urine toxicology screening was done on all methadone patients or only if clinically indicated (possible selection bias). Unclear sensitivity/specificity of promethazine urine tests using defined cut-offs.</p> <p>Convenience samples. Findings may not be broadly generalizable.</p>
Tsay, 2015 <sup>28</sup>	Exposure calls to U.S. poison control centers, 2002-2012	Retrospective review of intentional misuse or abuse exposure calls involving promethazine	<p>630 intentional misuse or abuse exposures involving a promethazine-containing product</p> <p>354 single product promethazine abuse or misuse exposures: Among these, 95 were promethazine single-ingredient product exposures and 259 promethazine combination product exposures (48% contained codeine, 46% contained DXM)</p> <p>Population rate doubled over 11-year time frame.</p>	<p>Data indicate that promethazine abuse and misuse occur, and the majority are single-product exposures, although predominantly involving combination products that contain other ingredients such as codeine and dextromethorphan.</p> <p>Did not look specifically at co-exposures with other opioids.</p> <p>Subject to limitations inherent to all poison control center call data (as</p>

Study	Population/setting	Design/Methods	Key Results	Comments/limitations
			<p>Most common clinical effects from nonmedical use of promethazine alone were drowsiness, agitation, and confusion.</p> <p>Combination products and exposures with co-ingestants (multi-substance exposures) were more likely to result in more serious outcomes requiring treatment. Not possible to discern whether related to additive effects or interactions, or primarily due to the inherent toxicity of the other substances.</p>	described in Discussion: Limitations of Data and Reviewed Studies section of this review).
Warner, 2016 <sup>27</sup>	National Vital Statistics System mortality files linked to electronic files containing literal text from death certificates, 2010-2014.	Review of drug mentions in deaths with underlying cause of death of drug overdose.	<p>In 2014, there were 3,274 overdose deaths involving hydrocodone. Of these, 80% involved one or more concomitant drugs (mean 2.4 additional drugs). 17% also involved alcohol.</p> <p>By comparison, in 2014, 5,417 deaths involved oxycodone, and 76% involved at least one other drug.</p> <p>The most common concomitant drugs with hydrocodone were alprazolam, oxycodone, diazepam, morphine, and heroin.</p>	<p>Numbers are likely an underestimate, as 19-30% of all drug overdose deaths have no mention of a specific drug.</p> <p>Variation in death investigation and documentation practices exist. Not all drugs are tested for in standard panels.</p>
Young, 2010 <sup>13</sup>	Rural (n=101) and urban (n=111) nonmedical prescription drug users in Kentucky	Cross-sectional study using interviewer-administered questionnaire and snowball sampling	<p>Of those who reported ever using hydrocodone non-medically, percent who reported having snorting it:</p> <ul style="list-style-type: none"> <li>• Urban (less severe addiction): 6.3%</li> <li>• Rural (more severe addiction): 74.3%</li> </ul> <p>Rural sample had more severe Addiction Severity Index scores and higher levels of drug abuse and non-oral routes overall.</p>	<p>Illustrates the wide range of drug abuse practices and route of abuse across different populations.</p> <p>Only included lifetime use, not recent or current use.</p> <p>Non-representative convenience sample</p>

Table generated by reviewer

**6.2 APPENDIX B. NPDS—DEFINITIONS OF EXPOSURE REASONS AND MEDICAL OUTCOMES, AND SECONDARY ANALYSIS RESULTS**

<b>NPDS Definitions for Intentional Exposure Reason Categories</b>	
<b>Intentional Exposure Reasons</b>	<b>NPDS Definition<sup>d</sup></b>
Suspected Suicides	“An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons.”
Abuse	“An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect”, including recreational use of a substance for any effect.
Misuse	“An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.”
Unknown	Exposures that are deemed to be intentional although the specific motive is undetermined.

<b>NPDS Definitions for Select Medical Outcomes</b>	
<b>Medical Outcomes</b>	<b>NPDS Definition<sup>e</sup></b>
No effect	No symptoms (clinical effects) as a result of the exposure
Minor effect	Some symptoms as a result of the exposure... minimally bothersome...symptoms usually resolve rapidly
Moderate effect <sup>a</sup>	Symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic...usually requiring treatment
Major effect <sup>a</sup>	Symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement
Death/Death, indirect report <sup>a</sup>	The patient died as a result of the exposure or as a direct complication of the exposure
<sup>a</sup> Analysis of medical outcomes included for exposures with a documented related clinical effect	

<sup>d</sup> American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016

<sup>e</sup> American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016

### **6.3 APPENDIX C: DESCRIPTION OF THE DRUG-INDUCED MORTALITY DATA SOURCE**

The drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality files, with drug-involved mortality information extracted from the death certificate literal text. The analytical dataset was constructed for analysis on October 6, 2016. The method used to extract information on drug-involved mortality has been described previously [Trinidad, 2016] and is briefly described here. The information written on the death certificate by the medical certifier on the cause, manner, circumstances, and other factors contributing to the death is referred to as the literal text fields. The literal text information had been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. For example, the drug “METHICILLIN” in the phrase “METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION” does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase “NOT DRUG RELATED” clearly indicates that a death did not involve drugs.

Although the drug-involved mortality data overcome a major limitation of the current coding system for mortality data by enabling the identification of specific drugs, the drug-involved mortality data have other limitations and considerations. These limitations and considerations are described in more detail elsewhere [Trinidad, 2016]. Most importantly, the quality of data extracted from death certificates depends on the amount and level of detail provided by medical certifiers, and such information can vary by certifier, jurisdiction, and over time. For example, the percent of drug overdose deaths with at least one mention of a specific drug has improved from 67% in 2010 to 78% in 2014 [Warner, 2016]. Undercounting of deaths with involvement of specific drugs is likely with the drug-involved mortality data.

## 6.4 APPENDIX D: NEISS-CADES 2016 ANALYSIS RESULTS

National Estimates of Emergency Department (ED) Visits for Pharmaceutical Adverse Events Attributed to Products Containing Hydrocodone, Promethazine, or Opioids with Non-selective Antihistamines, by Case Type, 2016 <sup>a</sup>												
Implicated Product(s)	Case Type											
	Abuse <sup>b</sup>		Self-harm/ Suicide Attempt <sup>c</sup>		Therapeutic Misuse <sup>d</sup>		Unknown Intent		Abuse, Self-harm/Suicide Attempt, Therapeutic Misuse, and Unknown Intent, Combined		Other Therapeutic Adverse Event <sup>e</sup>	
	Cases	Annual National Estimate	Cases	Annual National Estimate	Cases	Annual National Estimate	Cases	Annual National Estimate	Cases	Annual National Estimate	Cases	Annual National Estimate
	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
Any Hydrocodone-containing Product Implicated	73	5,093	127	9,268	34	3,365	87	8,287	321	26,013	249	23,388
Hydrocodone-containing Product Implicated Alone	30	2,075	50	3,784	22	2,082	32	2,792*	134	10,733	153	14,508
Any Promethazine-containing Product Implicated	18	--	13	--	1	--	8	--	40	2,883	27	2,307*
Promethazine-containing Product Implicated Alone	4	--	1	--	1	--	3	--	9	--	13	--
Opioid and Non-selective Antihistamine Both Implicated <sup>f</sup>	20	1,362	30	1,476	3	--	17	--	70	4,204	17	--

<sup>a</sup>Cases and national estimates based on data from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project, 2016.

<sup>b</sup>Clinician diagnosis of abuse, documentation of recreational use, or use to elicit a particular feeling

<sup>c</sup>Deliberate administration with the intent to die or to harm oneself

<sup>d</sup>Includes cases in which a therapeutic indication is specified, but the patient intentionally took a greater amount than prescribed/recommended, the patient took the medication more frequently than prescribed/recommended, the patient took medication that was not currently prescribed to him/her (e.g., took someone else's prescription medication), or other case details raise questions about veracity of the therapeutic intent (e.g., taking a very large amount "to sleep").

<sup>e</sup>Includes adverse effects, allergic reactions, supratherapeutic effects, medication errors, vaccination reactions, and secondary effects (e.g., choking, injection site reactions).

<sup>f</sup>Includes cases involving a combination product that contains an opioid and a non-selective antihistamine, and also cases involving 2 products -- an opioid-containing product and a non-selective antihistamine-containing product. For some cases (5 self-harm and 4 unknown intent cases), the specific opioid ingredients were not known and could include heroin. Also, for some non-therapeutic cases, the opioid ingredient may have been implicated based solely on laboratory testing.

\*Coefficient of variation >30%

Source: Data provided by the CDC Division of Healthcare Quality Promotion

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**Appendix 1**  
**Hydrocodone Bitartrate and Acetaminophen Labeling**

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**Addiction, Abuse, and Misuse**

Hydrocodonebitartrate and acetaminophen tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing hydrocodonebitartrate and acetaminophen tablets, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression may occur with use of hydrocodonebitartrate and acetaminophen tablets. Monitor for respiratory depression especially during initiation of hydrocodonebitartrate and acetaminophen tablets or following a dose increase [see WARNINGS].

**Accidental Ingestion**

Accidental ingestion of hydrocodonebitartrate and acetaminophen tablets, especially by children, can result in a fatal overdose of hydrocodonebitartrate and acetaminophen tablets [see WARNINGS].

**Neonatal Opioid Withdrawal Syndrome**

Prolonged use of hydrocodonebitartrate and acetaminophen tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see WARNINGS].

**Cytochrome P450 3A4 Interaction**

The concomitant use of hydrocodonebitartrate and acetaminophen tablets with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentrations. Monitor patients receiving hydrocodonebitartrate and acetaminophen tablets and any cytochrome P450 3A4 inhibitor or inducer for signs of respiratory depression or sedation [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

**Hepatotoxicity**

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product [see WARNINGS, OVERDOSAGE].

**Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

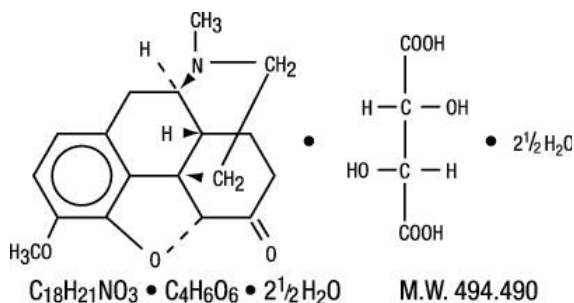
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see WARNINGS, PRECAUTIONS; Drug Interactions].

- Reserve concomitant prescribing of hydrocodonebitartrate and acetaminophen tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation

**DESCRIPTION**

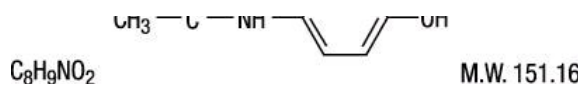
Hydrocodone bitartrate and acetaminophen are available in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 $\alpha$ -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:





Each Hydrocodone Bitartrate and Acetaminophen Tablet contains:

Hydrocodone Bitartrate..... 2.5 mg

Acetaminophen..... 325 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid.

This product complies with USP dissolution test 2.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Hydrocodone is a full opioid agonist with relative selectivity for the mu-opioid ( $\mu$ ) receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

The precise mechanism of the analgesic properties of acetaminophen is not established but is thought to involve central actions.

### Pharmacodynamics

#### Effects on the Central Nervous System

The principal therapeutic action of hydrocodone is analgesia. Hydrocodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

#### Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

#### Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

#### Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see **ADVERSE REACTIONS**]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see **ADVERSE REACTIONS**].

#### Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

#### Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see **DOSAGE AND ADMINISTRATION**].

#### Concentration-Adverse Reaction Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see **DOSAGE AND ADMINISTRATION**].

## Pharmacokinetics

The behavior of the individual components is described below.

### Hydrocodone

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was  $23.6 \pm 5.2$  ng/mL. Maximum serum levels were achieved at  $1.3 \pm 0.3$  hours and the half-life was determined to be  $3.8 \pm 0.3$  hours.

Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- $\alpha$ - and 6- $\beta$ -hydroxymetabolites. See **OVERDOSAGE** for toxicity information.

CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone. Hydromorphone is formed from the O-demethylation of hydrocodone and may contribute to the total analgesic effect of hydrocodone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs [see **PRECAUTIONS; Drug Interactions**]. N-demethylation of hydrocodone to form norhydrocodone via CYP3A4 while O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme. Hydrocodone and its metabolites are eliminated primarily in the kidneys.

### Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. A small fraction (10-25%) of acetaminophen is bound to plasma proteins. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

## INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

### Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see **WARNINGS**], reserve hydrocodone bitartrate and acetaminophen tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics):

- have not been tolerated, or are not expected to be tolerated,
- have not provided adequate analgesia, or are not expected to provide adequate analgesia

## CONTRAINDICATIONS

Hydrocodone bitartrate and acetaminophen tablets are contraindicated in patients with:

- Significant respiratory depression [see **WARNINGS**]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see **WARNINGS**]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see **WARNINGS**]
- Hypersensitivity to hydrocodone or acetaminophen (e.g., anaphylaxis) [see **WARNINGS, ADVERSE REACTIONS**]

## WARNINGS

### **Addiction, Abuse, and Misuse**

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a Schedule II controlled substance. As an opioid, hydrocodone bitartrate and acetaminophen tablets expose users to the risks of addiction, abuse, and misuse [see **DRUG ABUSE AND DEPENDENCE**].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydrocodone bitartrate and acetaminophen tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing hydrocodone bitartrate and acetaminophen tablets, and monitor all patients receiving hydrocodone bitartrate and acetaminophen tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as hydrocodone bitartrate and acetaminophen tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydrocodone bitartrate and acetaminophen tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing hydrocodone bitartrate and acetaminophen tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see **PRECAUTIONS; Information for Patients/Caregivers**]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

### Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see **OVERDOSAGE**]. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of hydrocodone bitartrate and acetaminophen tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of hydrocodone bitartrate and acetaminophen tablets.

To reduce the risk of respiratory depression, proper dosing and titration of hydrocodone bitartrate and acetaminophen tablets are essential [see **DOSAGE AND ADMINISTRATION**]. Overestimating the hydrocodone bitartrate and acetaminophen tablets dosage when converting patients from another opioid product can result in a fatal overdose.

Accidental ingestion of hydrocodone bitartrate and acetaminophen tablets, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone bitartrate and acetaminophen tablets.

### Neonatal Opioid Withdrawal Syndrome

Prolonged use of hydrocodone bitartrate and acetaminophen tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see **PRECAUTIONS; Information for Patients/Caregivers, Pregnancy**].

### Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of hydrocodone bitartrate and acetaminophen tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of hydrocodone bitartrate and acetaminophen tablets and prolong opioid adverse reactions, and which may cause potentially fatal respiratory depression [see **WARNINGS**], particularly when an inhibitor is added after a stable dose of hydrocodone bitartrate and acetaminophen tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in hydrocodone bitartrate and acetaminophen tablets-treated patients may increase hydrocodone plasma concentrations and prolong opioid adverse reactions. When adding CYP3A4 inhibitors or discontinuing CYP3A4 inducers in hydrocodone bitartrate and acetaminophen tablets-treated patients, follow patients at frequent intervals and consider dosage reduction of hydrocodone bitartrate and acetaminophen tablets until stable drug effects are achieved [see **PRECAUTIONS; Drug Interactions**].

Concomitant use of hydrocodone bitartrate and acetaminophen tablets with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease hydrocodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using hydrocodone bitartrate and acetaminophen tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, follow patients at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see **PRECAUTIONS; Drug Interactions**].

### Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of hydrocodone bitartrate and acetaminophen tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see **PRECAUTIONS; Drug Interactions**].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when hydrocodone bitartrate and acetaminophen tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see **PRECAUTIONS; Drug Interactions, Information for Patients/Caregivers**].

### Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of hydrocodone bitartrate and acetaminophen tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

**Patients with Chronic Pulmonary Disease:** Hydrocodone bitartrate and acetaminophen tablet-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of hydrocodone bitartrate and acetaminophen tablets [see **WARNINGS; Life-Threatening Respiratory Depression**].

**Elderly, Cachetic, or Debilitated Patients:** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see **WARNINGS; Life-Threatening Respiratory Depression**].

Follow such patients closely, particularly when initiating and titrating hydrocodone bitartrate and acetaminophen tablets and when hydrocodone bitartrate and acetaminophen tablets are given concomitantly with other drugs that depress respiration [see **WARNINGS; Life-Threatening Respiratory Depression**]. Alternatively, consider the use of non-opioid analgesics in these patients.

#### **Adrenal Insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

#### **Severe Hypotension**

Hydrocodone bitartrate and acetaminophen tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see **PRECAUTIONS; Drug Interactions**]. Follow these patients for signs of hypotension after initiating or titrating the dosage of hydrocodone bitartrate and acetaminophen tablets. In patients with circulatory shock hydrocodone bitartrate and acetaminophen tablets may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of hydrocodone bitartrate and acetaminophen tablets with circulatory shock.

#### **Hepatotoxicity**

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of acetaminophen per day, even if they feel well.

#### **Serious Skin Reactions**

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

#### **Hypersensitivity/Anaphylaxis**

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue hydrocodone bitartrate and acetaminophen tablets immediately and seek medical care if they experience these symptoms. Do not prescribe hydrocodone bitartrate and acetaminophen tablets for patients with acetaminophen allergy [see **PRECAUTIONS; Information for Patients/Caregivers**].

#### **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), hydrocodone bitartrate and acetaminophen tablets may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Follow such patients for signs of sedation and respiratory depression, particularly when initiating therapy with hydrocodone bitartrate and acetaminophen tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of hydrocodone bitartrate and acetaminophen tablets in patients with impaired consciousness or coma.

#### **Risks of Use in Patients with Gastrointestinal Conditions**

Hydrocodone bitartrate and acetaminophen tablets are contraindicated in patients with gastrointestinal obstruction, including paralytic ileus.

The administration of hydrocodone bitartrate and acetaminophen tablets or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Hydrocodone may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

#### **Increased Risk of Seizures in Patients with Seizure Disorders**

The hydrocodone in hydrocodone bitartrate and acetaminophen tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Follow patients with a history of seizure disorders for worsened seizure control during hydrocodone bitartrate and acetaminophen tablet therapy.

## Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including hydrocodone bitartrate and acetaminophen tablets. In these patients, mixed agonist/antagonist and partial analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing hydrocodone bitartrate and acetaminophen tablets, gradually taper the dosage [see **DOSAGE AND ADMINISTRATION**]. Do not abruptly discontinue hydrocodone bitartrate and acetaminophen tablets [see **DRUG ABUSE AND DEPENDENCE**] in patients who have been using hydrocodone bitartrate and acetaminophen tablets around the clock for more than 5 days.

## PRECAUTIONS

### Risks of Driving and Operating Machinery

Hydrocodone bitartrate and acetaminophen tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of hydrocodone bitartrate and acetaminophen tablets and know how they will react to the medication [see **PRECAUTIONS; Information for Patients/Caregivers**].

### Information for Patients/Caregivers

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Addiction, Abuse, and Misuse

Inform patients that the use of hydrocodone bitartrate and acetaminophen tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see **WARNINGS**]. Instruct patients not to share hydrocodone bitartrate and acetaminophen tablets with others and to take steps to protect hydrocodone bitartrate and acetaminophen tablets from theft or misuse.

#### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting hydrocodone bitartrate and acetaminophen tablets or when the dosage is increased, and that it can occur even at recommended dosages [see **WARNINGS**]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

#### Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see **WARNINGS**]. Instruct patients to take steps to store hydrocodone bitartrate and acetaminophen tablets securely and to dispose of unused hydrocodone bitartrate and acetaminophen tablets by flushing down the toilet.

#### Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if hydrocodone bitartrate and acetaminophen tablets are used with benzodiazepines and other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see **WARNINGS, PRECAUTIONS; Drug Interactions**].

#### Serotonin Syndrome

Inform patients that hydrocodone bitartrate and acetaminophen tablets could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications [see **PRECAUTIONS; Drug Interactions**].

#### Monoamine Oxidase Inhibitor (MAOI) Interaction

Inform patients to avoid taking hydrocodone bitartrate and acetaminophen tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking hydrocodone bitartrate and acetaminophen tablets [see **PRECAUTIONS; Drug Interactions**].

#### Adrenal Insufficiency

Inform patients that hydrocodone bitartrate and acetaminophen tablets could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see **WARNINGS**].

#### Important Administration Instructions

Instruct patients how to properly take hydrocodone bitartrate and acetaminophen tablets [see **DOSAGE AND ADMINISTRATION, WARNINGS**].

#### Maximum Daily Dose of Acetaminophen

Inform patients not to take more than 4000 milligrams of acetaminophen per day. Advise patients to call their prescriber if they take more than the recommended dose.

#### Hypotension

Inform patients that hydrocodone bitartrate and acetaminophen tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see **WARNINGS**].

#### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in hydrocodone bitartrate and acetaminophen tablets. Advise patients how to recognize such a reaction and when to seek medical attention [see **CONTRAINDICATIONS, ADVERSE REACTIONS**].

Pregnancy*Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that prolonged use of hydrocodone bitartrate and acetaminophen tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see **WARNINGS, PRECAUTIONS; Pregnancy**].

*Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that hydrocodone bitartrate and acetaminophen tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see **PRECAUTIONS; Pregnancy**].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see **PRECAUTIONS; Nursing Mothers**].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**].

Driving or Operating Heavy Machinery

Inform patients that hydrocodone bitartrate and acetaminophen tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see **WARNINGS**].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see **ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**].

Disposal of Unused Hydrocodone Bitartrate and Acetaminophen Tablets

Advise patients to dispose of unused hydrocodone bitartrate and acetaminophen tablets by flushing unused tablets down the toilet.

**Laboratory Tests**

In patients with severe hepatic or renal disease, effects of therapy should be followed with serial liver and/or renal function tests.

**Drug Interactions**Inhibitors of CYP3A4 and CYP2D6

The concomitant use of hydrocodone bitartrate and acetaminophen tablets and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), can increase the plasma concentration of the hydrocodone from hydrocodone bitartrate and acetaminophen tablets, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of hydrocodone bitartrate and acetaminophen tablets and both CYP3A4 and CYP2D6 inhibitors, particularly when an inhibitor is added after a stable dose of hydrocodone bitartrate and acetaminophen tablets is achieved [see **WARNINGS**].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease [see **CLINICAL PHARMACOLOGY**], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone bitartrate and acetaminophen tablets.

If concomitant use is necessary, consider dosage reduction of hydrocodone bitartrate and acetaminophen tablets until stable drug effects are achieved. Follow patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the hydrocodone bitartrate and acetaminophen tablets dosage until stable drug effects are achieved. Follow for signs or symptoms of opioid withdrawal.

Inducers of CYP3A4

The concomitant use of hydrocodone bitartrate and acetaminophen tablets and CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of hydrocodone [see **CLINICAL PHARMACOLOGY**], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone [see **WARNINGS**].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase [see **CLINICAL PHARMACOLOGY**], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the hydrocodone bitartrate and acetaminophen tablets dosage until stable drug effects are achieved. Follow the patient for signs and symptoms of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider hydrocodone bitartrate and acetaminophen tablets dosage reduction and follow for signs of respiratory depression.

Benzodiazepines and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants, such as benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see **WARNINGS**].

Serotonergic Drugs



The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome [see **PRECAUTIONS; Information for Patients/Caregivers**].

If concomitant use is warranted, carefully follow the patient, particularly during treatment initiation and dose adjustment. Discontinue hydrocodone bitartrate and acetaminophen tablets if serotonin syndrome is suspected.

#### Monoamine Oxidase Inhibitors (MAOIs)

The concomitant use of opioids and MAOIs, such as phenelzine, tranylcypromine, or linezolid, may manifest as serotonin syndrome, or opioid toxicity (e.g., respiratory depression, coma) [see **WARNINGS**].

The use of hydrocodone bitartrate and acetaminophen tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

#### Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

The concomitant use of opioids with other opioid analgesics, such as butorphanol, nalbuphine, pentazocine, may reduce the analgesic effect of hydrocodone bitartrate and acetaminophen tablets and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

#### Muscle Relaxants

Hydrocodone bitartrate and acetaminophen tablets may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

If concomitant use is warranted, monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of hydrocodone bitartrate and acetaminophen tablets and/or the muscle relaxant as necessary.

#### Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

If concomitant use is warranted, follow patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

#### Anticholinergic Drugs

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

If concomitant use is warranted, follow patients for signs and symptoms of urinary retention or reduced gastric motility when hydrocodone bitartrate and acetaminophen tablets are used concomitantly with anticholinergic drugs.

#### **Drug/Laboratory Test Interactions**

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

##### Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of the combination of hydrocodone bitartrate and acetaminophen tablets have not been conducted.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.2-1.4 times the MHDD, based on a body surface area comparison.

##### Mutagenesis

In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

##### Impairment of Fertility

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.78 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

**Infertility**

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see **ADVERSE REACTIONS**].

**Pregnancy****Teratogenic Effects***Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects***Fetal/Neonatal Adverse Reactions*

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity, abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see **WARNINGS**].

**Labor or Delivery**

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Hydrocodone bitartrate and acetaminophen tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including hydrocodone bitartrate and acetaminophen tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

**Nursing Mothers**

Hydrocodone is present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for hydrocodone bitartrate and acetaminophen tablets and any potential adverse effects on the breastfed infant from hydrocodone bitartrate and acetaminophen tablets or from the underlying maternal condition.

Infants exposed to hydrocodone bitartrate and acetaminophen tablets through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

**Pediatric Use**

Safety and effectiveness of hydrocodone bitartrate and acetaminophen tablets in pediatric patients have not been established.

**Geriatric Use**

Elderly patients (aged 65 years or older) may have increased sensitivity to hydrocodone bitartrate and acetaminophen tablets. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of hydrocodone bitartrate and acetaminophen tablets slowly in geriatric patients and follow closely for signs of central nervous system and respiratory depression [see **WARNINGS**].

Hydrocodone and acetaminophen are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

**Hepatic Impairment**

Patients with hepatic impairment may have higher plasma hydrocodone concentrations than those with normal function. Use a low initial dose of hydrocodone bitartrate and acetaminophen tablets in patients with hepatic impairment and follow closely for adverse events such as respiratory depression and sedation.

**Renal Impairment**

Patients with renal impairment may have higher plasma hydrocodone concentrations than those with normal function. Use a low initial dose hydrocodone bitartrate and acetaminophen tablets in patients with renal impairment and follow closely for adverse events such as respiratory depression and sedation.

**ADVERSE REACTIONS**

The following adverse reactions have been identified during post approval use of hydrocodone and acetaminophen tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting.

Other adverse reactions include:

**Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychological dependence, mood changes.

**Gastrointestinal System:** Constipation.

**Genitourinary System:** Ureteral spasm, spasm of vesical sphincters, and urinary retention.

**Special Senses:** Cases of hearing impairment or permanent loss have been reported predominately in patients with chronic overdose.

**Dermatological:** Skin rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, allergic reactions.

**Hematological:** Thrombocytopenia, agranulocytosis.

- **Serotonin syndrome:** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
- **Adrenal insufficiency:** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- **Anaphylaxis:** Anaphylaxis has been reported with ingredients contained in hydrocodone bitartrate and acetaminophen tablets.
- **Androgen deficiency:** Cases of androgen deficiency have occurred with chronic use of opioids [see **CLINICAL PHARMACOLOGY**].

## DRUG ABUSE AND DEPENDENCE

### Controlled Substance

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a Schedule II controlled substance.

### Abuse

Hydrocodone bitartrate and acetaminophen tablets contain hydrocodone, a substance with a high potential for abuse similar to other opioids, including fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol, can be abused and are subject to misuse, addiction, and criminal diversion [see **WARNINGS**].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Hydrocodone bitartrate and acetaminophen tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

### Risks Specific to Abuse of Hydrocodone Bitartrate and Acetaminophen Tablets

Hydrocodone bitartrate and acetaminophen tablets are for oral use only. Hydrocodone bitartrate and acetaminophen tablets pose a risk of overdose and death. The risk is increased with concurrent abuse of hydrocodone bitartrate and acetaminophen tablets with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

### Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Hydrocodone bitartrate and acetaminophen tablets should not be abruptly discontinued in a physically dependent patient [see **DOSAGE AND ADMINISTRATION**]. If hydrocodone bitartrate and acetaminophen tablets are abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see **PRECAUTIONS; Pregnancy**].

## **OVERDOSAGE**

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

### **Clinical Presentation**

Acute overdosage with hydrocodone bitartrate and acetaminophen tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

#### *Acetaminophen*

Dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect of acetaminophen overdosage. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

### **Treatment of Overdose**

#### Hydrocodone

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydrocodone bitartrate and acetaminophen tablets overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydrocodone bitartrate and acetaminophen tablets overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of hydrocodone in hydrocodone bitartrate and acetaminophen tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

#### Acetaminophen

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

## **DOSAGE AND ADMINISTRATION**

### **Important Dosage and Administration Instructions**

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see **WARNINGS**].

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see **WARNINGS**].

Follow patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with hydrocodone bitartrate and acetaminophen tablets and adjust the dosage accordingly [see **WARNINGS**].

### **Initial Dosage**

### Initiating Treatment with Hydrocodone Bitartrate and Acetaminophen Tablets

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 12 tablets.

### Conversion from Other Opioids to Hydrocodone Bitartrate and Acetaminophen Tablets

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of hydrocodone bitartrate and acetaminophen tablets. It is safer to underestimate a patient's 24-hour hydrocodone bitartrate and acetaminophen tablets dosage than to overestimate the 24-hour hydrocodone bitartrate and acetaminophen tablets dosage and manage an adverse reaction due to overdose.

### Conversion from Hydrocodone Bitartrate and Acetaminophen Tablets to Extended-Release Hydrocodone

The relative bioavailability of hydrocodone from hydrocodone bitartrate and acetaminophen tablets compared to extended-release hydrocodone products is unknown, so conversion to extended-release products must be accompanied by close observation for signs of excessive sedation and respiratory depression.

### **Titration and Maintenance of Therapy**

Individually titrate hydrocodone bitartrate and acetaminophen tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydrocodone bitartrate and acetaminophen tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see **WARNINGS**]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the hydrocodone bitartrate and acetaminophen tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

### **Discontinuation of Hydrocodone Bitartrate and Acetaminophen Tablets**

When a patient who has been taking hydrocodone bitartrate and acetaminophen tablets regularly and may be physically dependent no longer requires therapy with hydrocodone bitartrate and acetaminophen tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue hydrocodone bitartrate and acetaminophen tablets in a physically-dependent patient [see **WARNINGS, DRUG ABUSE AND DEPENDENCE**].

### **HOW SUPPLIED**

Hydrocodone Bitartrate and Acetaminophen Tablets, USP are supplied as white, capsule-shaped tablets containing 2.5 mg hydrocodone bitartrate (**WARNING: May be habit-forming**) and 325 mg acetaminophen. Tablets are debossed with "2.5/325" on one side and "ADG" on the other side, and are supplied in bottles of 100 tablets, NDC 46672-092-10, and 500 tablets, NDC 46672-092-50.

Store at 20 to 25 C (68 to 77 F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.

Manufactured by:

**Mikart, Inc.**

Atlanta, GA 30318

### **Medication Guide**

MEDICATION GUIDE	
<b>Hydrocodone Bitartrate</b> (hye" droe koe' done bye tar trate) <b>and Acetaminophen</b> (a seet"a min' oh fen) <b>Tablets USP, CII</b>	
<b>Hydrocodone Bitartrate and Acetaminophen Tablets are:</b>	
<ul style="list-style-type: none"> <li>• A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid pain medicine, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.</li> <li>• An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.</li> </ul>	
<b>Important information about Hydrocodone Bitartrate and Acetaminophen Tablets:</b>	
<ul style="list-style-type: none"> <li>• <b>Get emergency help right away if you take too much Hydrocodone Bitartrate and Acetaminophen Tablets (overdose).</b> When you first start taking Hydrocodone Bitartrate and Acetaminophen Tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.</li> <li>• Taking Hydrocodone Bitartrate and Acetaminophen Tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.</li> <li>• Never give anyone else your Hydrocodone Bitartrate and Acetaminophen Tablets. They could die from taking it. Store Hydrocodone Bitartrate and Acetaminophen Tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away Hydrocodone Bitartrate and Acetaminophen Tablets is against the law.</li> </ul>	
<b>Do not take Hydrocodone Bitartrate and Acetaminophen Tablets if you have:</b>	

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known hypersensitivity to hydrocodone or acetaminophen, or any ingredient in Hydrocodone Bitartrate and Acetaminophen Tablets

**Before taking Hydrocodone Bitartrate and Acetaminophen Tablets, tell your healthcare provider if you have a history of:**

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

**Tell your healthcare provider if you are:**

- **pregnant or planning to become pregnant.** Prolonged use of Hydrocodone Bitartrate and Acetaminophen Tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Hydrocodone bitartrate and acetaminophen pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking Hydrocodone Bitartrate and Acetaminophen Tablets with certain other medicines can cause serious side effects that could lead to death.

**When taking Hydrocodone Bitartrate and Acetaminophen Tablets:**

- Do not change your dose. Take Hydrocodone Bitartrate and Acetaminophen Tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every four to six hours as needed for pain.
- Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking Hydrocodone Bitartrate and Acetaminophen Tablets regularly, do not stop taking Hydrocodone Bitartrate and Acetaminophen Tablets without talking to your healthcare provider.
- After you stop taking Hydrocodone Bitartrate and Acetaminophen Tablets, the unused tablets should be disposed of by flushing down the toilet.

**While taking Hydrocodone Bitartrate and Acetaminophen Tablets DO NOT:**

- Drive or operate heavy machinery, until you know how Hydrocodone Bitartrate and Acetaminophen Tablets affect you. Hydrocodone Bitartrate and Acetaminophen Tablets can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with Hydrocodone Bitartrate and Acetaminophen Tablets may cause you to overdose and die.

**The possible side effects of Hydrocodone Bitartrate and Acetaminophen Tablets:**

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

**Get emergency medical help if you have:**

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of Hydrocodone Bitartrate and Acetaminophen Tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to [dailymed.nlm.nih.gov](http://dailymed.nlm.nih.gov)**

Manufactured by: Mikart, Inc., Atlanta, GA 30318

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 11/2016

Code 1017Z00

**MEDICATION GUIDE**

**Package/Label Display Panel**

NDC 46672-092-10	<b>PHARMACIST:</b> Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.
<b>Hydrocodone Bitartrate and Acetaminophen</b>	<b>USUAL DOSAGE:</b> See package insert for

**Tablets, USP**  
**2.5 mg/325 mg**



complete dosage recommendations.

Keep this and all medication out of the reach of children.

Each debossed white tablet contains:  
 Hydrocodone Bitartrate, USP..... 2.5 mg  
 WARNING: May be habit-forming.  
 Acetaminophen, USP..... 325 mg

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

Manufactured by:  
**MIKART, INC.**  
 Atlanta, GA 30318



Dispense the accompanying Medication Guide to each patient.

**Rx only**

Contents: 100 Tablets

Code 1017Z10

Rev. 09/16

**HYDROCODONE BITARTRATE AND ACETAMINOPHEN**

hydrocodone bitartrate and acetaminophen tablet

**Product Information**

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:46672-092
Route of Administration	ORAL	DEA Schedule	CII

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII: 6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	2.5 mg
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII: 362O9ITL9D)	ACETAMINOPHEN	325 mg

**Inactive Ingredients**

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSPVIDONE (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6130)	
POVIDONES (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

**Product Characteristics**

Color	WHITE	Score	no score
Shape	OVAL (CAPSULE)	Size	14mm
Flavor		Imprint Code	25;325;ADG
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46672-092-10	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/09/2010	
2	NDC:46672-092-50	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/09/2010	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040846	06/09/2010	

**Labeler** - Mikart, Inc (030034847)

Revised: 12/2016

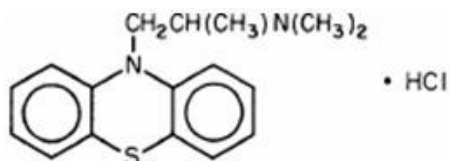
Mikart, Inc

**Appendix 2**  
**Promethazine Labeling**



## DESCRIPTION

Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10 *H*-Phenothiazine-10-ethanamine, *N,N*, $\alpha$ -trimethyl-,monohydrochloride, ( $\pm$ )- with the following structural formula:



Promethazine hydrochloride is a racemic compound; the molecular formula is  $C_{17}H_{20}N_2S \cdot HCl$  and its molecular weight is 320.88.

Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is freely soluble in water and soluble in alcohol.

Each tablet for oral administration contains 12.5 mg, 25 mg or 50 mg promethazine hydrochloride, USP. The inactive ingredients include: hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The 12.5 mg contains FD&C Yellow No.6 aluminum lake. The 50 mg contains D&C Red Lake Blend No.27 aluminum lake and D & C Red No. 30 aluminum lake.

## CLINICAL PHARMACOLOGY

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties.

Promethazine is an  $H_1$  receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects.

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and *N*-demethylpromethazine are the predominant metabolites appearing in the urine.

## INDICATIONS AND USAGE

Promethazine hydrochloride tablets are useful for:

Perennial and seasonal allergic rhinitis.

Vasomotor rhinitis.

Allergic conjunctivitis due to inhalant allergens and foods.

Mild, uncomplicated allergic skin manifestations of urticaria and angioedema. Amelioration of allergic reactions to blood or plasma.

Dermographism.

Anaphylactic reactions as adjunctive therapy to epinephrine and other standard measures after the acute manifestations have been controlled.

Preoperative, postoperative, or obstetric sedation.

Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.

Therapy adjunctive to meperidine or other analgesics for control of postoperative pain.

Sedation in both children and adults as well as relief of apprehension and production of light sleep from which the

patient can be easily aroused.

Active and prophylactic treatment of motion sickness.

Antiemetic therapy in postoperative patients.

## CONTRAINDICATIONS

Promethazine hydrochloride tablets are contraindicated for use in pediatric patients less than two years of age.

Promethazine hydrochloride tablets are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

## WARNINGS

**PROMETHAZINE HCl SHOULD NOT BE USED IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION.**

**POSTMARKETING CASES OF RESPIRATORY DEPRESSION, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH USE OF PROMETHAZINE HCl IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PROMETHAZINE HCl HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS.**

**CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HCl TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THAT THE LOWEST EFFECTIVE DOSE OF PROMETHAZINE HCl BE USED IN PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHER DRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.**

### CNS Depression

Promethazine HCl tablets may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore, such agents should either be eliminated or given in reduced dosage in the presence of promethazine HCl (see [PRECAUTIONS: Information for Patients](#) and [Drug Interactions](#)).

### Respiratory Depression

Promethazine HCl tablets may lead to potentially fatal respiratory depression.

Use of promethazine HCl tablets in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.

### Lower Seizure Threshold

Promethazine HCl tablets may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

### Bone-Marrow Depression

Promethazine HCl tablets should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when promethazine HCl has been used in association with other known marrow-toxic agents.

### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been

reported in association with promethazine HCl alone or in combination with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of promethazine HCl, antipsychotic drugs, if any, and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Since recurrences of NMS have been reported with phenothiazines, the reintroduction of promethazine HCl should be carefully considered.

### Use in Pediatric Patients

**PROMETHAZINE HCl TABLETS ARE CONTRAINDICATED FOR THE USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.**

**CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HCl TABLETS TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION. RESPIRATORY DEPRESSION AND APNEA, SOMETIMES ASSOCIATED WITH DEATH, ARE STRONGLY ASSOCIATED WITH PROMETHAZINE PRODUCTS AND ARE NOT DIRECTLY RELATED TO INDIVIDUALIZED WEIGHT-BASED DOSING, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION, CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS.**

**ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PROMETHAZINE HCl TABLETS ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PROMETHAZINE HCl TABLETS SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.**

Excessively large dosages of antihistamines, including promethazine HCl tablets in pediatric patients may cause sudden death (see **OVERDOSAGE**). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine HCl in pediatric patients. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl.

### Other Considerations

Administration of promethazine HCl has been associated with reported cholestatic jaundice.

## PRECAUTIONS

### General

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Promethazine HCl tablets should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

### Information for Patients

Promethazine HCl tablets may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol or

other central-nervous system depressants such as sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers, may enhance impairment (see **WARNINGS: CNS Depression** and **PRECAUTIONS: Drug Interactions**). Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Avoid prolonged exposure to the sun.

A patient information leaflet is included and summarizes important information about promethazine.

### **Drug Interactions**

*CNS Depressants:* Promethazine HCl tablets may increase, prolong, or intensify the sedative action of other central-nervous system depressants, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine HCl. When given concomitantly with promethazine HCl tablets, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

*Epinephrine:* Because of the potential for promethazine HCl to reverse epinephrine's vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine HCl tablets overdose.

*Anticholinergics:* Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

*Monoamine Oxidase Inhibitors (MAOI):* Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. This possibility should be considered with promethazine HCl tablets.

### **Drug/Laboratory Test Interactions**

The following laboratory tests may be affected in patients who are receiving therapy with promethazine HCl.

*Pregnancy Tests:* Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

*Glucose Tolerance Test:* An increase in blood glucose has been reported in patients receiving promethazine HCl.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

### **Pregnancy**

*Teratogenic Effects: Pregnancy Category C:* Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 mg/kg and 12.5 mg/kg of promethazine HCl. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women.

Promethazine HCl tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nonteratogenic Effects:* Promethazine administered to a pregnant women within two weeks of delivery may inhibit platelet aggregation in the newborn.

### **Labor and Delivery**

Promethazine HCl may be used alone or as an adjunct to narcotic analgesics during labor (see **DOSAGE AND ADMINISTRATION**). Limited data suggest that use of promethazine HCl during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also *Nonteratogenic Effects*.)

### **Nursing Mothers**

It is not known whether promethazine HCl is excreted in human milk. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants from promethazine HCl tablets a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Pediatric Use**

**PROMETHAZINE HYDROCHLORIDE TABLETS ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE (See **WARNINGS: Black Box Warning and Use in Pediatric Patients**).**

Promethazine HCl tablets should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS: Use in Pediatric Patients**).

### **Geriatric Use**

Clinical studies of promethazine HCl formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of promethazine HCl tablets and observed closely.

## **ADVERSE REACTIONS**

### **Central Nervous System**

Drowsiness is the most prominent CNS effect of this drug. Sedation, somnolence, blurred vision, dizziness; confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion; lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria. Hallucinations have also been reported.

### **Cardiovascular**

Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

### **Dermatologic**

Dermatitis, photosensitivity, urticaria.

### **Hematologic**

Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

### **Gastrointestinal**

Dry mouth, nausea, vomiting, jaundice.

### **Respiratory**

Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal). (See **WARNINGS: Respiratory Depression**.)

## Other

Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported. (See **WARNINGS: Neuroleptic Malignant Syndrome.** )

## Paradoxical Reactions

Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Consideration should be given to the discontinuation of promethazine HCl and to the use of other drugs if these reactions occur. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

## OVERDOSAGE

Signs and symptoms of overdose with promethazine HCl range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness, and sudden death. Other reported reactions include hyperreflexia, hypertonia, ataxia, athetosis, and extensor-plantar reflexes (Babinski reflex).

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical-type reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms - dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms - may occur.

## Treatment

Treatment of overdose is essentially symptomatic and supportive. Only in cases of extreme overdose or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine HCl are not reversed by naloxone. Avoid analeptics which may cause convulsions.

The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of norepinephrine or phenylephrine should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. Oxygen may also be administered.

Limited experience with dialysis indicates that it is not helpful.

## DOSAGE AND ADMINISTRATION

**Promethazine hydrochloride tablets are contraindicated for children under 2 years of age (see **WARNINGS: Black Box Warning and Use in Pediatric Patients.**)**

## Allergy

The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Single 25 mg doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The administration of promethazine HCl in 25 mg doses will control minor transfusion reactions of an allergic nature.

## Motion Sickness

The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated eight to twelve hours later, if necessary. On succeeding days of travel, it is

recommended that 25 mg be given on arising and again before the evening meal. For children, promethazine hydrochloride tablets 12.5 to 25 mg, twice daily, may be administered.

### Nausea and Vomiting

Antiemetics should not be used in vomiting of unknown etiology in children and adolescents (see **WARNINGS: Use in Pediatric Patients**).

The average effective dose of promethazine HCl for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (promethazine injection) or by rectal suppository. 12.5 mg to 25 mg doses may be repeated, as necessary, at four-to six-hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg per pound of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at four-to-six hour intervals, as necessary.

### Sedation

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg promethazine HCl by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.

### Pre- and Postoperative Use

Promethazine HCl in 12.5 to 25 mg doses for children and 50 mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication, children require doses of 0.5 mg per pound of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug.

Usual adult dosage is 50 mg promethazine HCl with an appropriately reduced dose of narcotic or barbiturate and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5 to 25 mg in children and 25 to 50 mg doses in adults.

Promethazine hydrochloride tablets are contraindicated for children under 2 years of age.

### HOW SUPPLIED

Promethazine hydrochloride tablets, USP contains 12.5 mg, 25 mg or 50 mg as promethazine hydrochloride, USP and are supplied as follows:

**12.5 mg:** Light peach, round, biconvex, uncoated tablets, debossed "107" on one side and scored on the other side.

NDC	57664-107-83	Bottles of 30	CRC
NDC	57664-107-88	Bottles of 100	CRC
NDC	57664-107-08	Bottles of 100	
NDC	57664-107-13	Bottles of 500	
NDC	57664-107-18	Bottles of 1000	

**25 mg:** White to off-white, round, flat face bevel edge, uncoated tablets, debossed "108" on one side and scored on the other side.

NDC	57664-108-83	Bottles of 30	CRC
NDC	57664-108-88	Bottles of 100	CRC
NDC	57664-108-08	Bottles of 100	
NDC	57664-108-13	Bottles of 500	
NDC	57664-108-18	Bottles of 1000	

**50 mg:** Light pink, round, biconvex, uncoated tablets, debossed "109" on one side and plain on the other side.

NDC	57664-109-83	Bottles of 30	CRC
NDC	57664-109-88	Bottles of 100	CRC

NDC	57664-109-08	Bottles of 100
NDC	57664-109-13	Bottles of 500
NDC	57664-109-18	Bottles of 1000

Store at 20° - 25°C (68° - 77°F). (See USP Controlled Room Temperature).

Dispense in tight, light-resistant container.

**Distributed by: Sun Pharmaceutical Industries, Inc.  
Cranbury, NJ 08512**

6044T04

Rev. 07/2014

## PATIENT INFORMATION LEAFLET

### PROMETHAZINE HYDROCHLORIDE TABLETS

#### Rx only

#### What Is Promethazine HCl Tablets?

Promethazine is an antihistamine which can be taken by mouth as a tablet or syrup, rectally as a suppository, or by injection. It can be used for:

- “hay fever,” or, a stuffy runny nose from allergy
- watery, itchy eyes due to inhaled allergies and foods
- mild allergic skin reactions with itching and swelling
- allergic reactions to blood or plasma
- dermatographism, a form of hives known as “skin writing”
- serious allergic reactions along with epinephrine and other treatments
- sedation before or after surgery, or during childbirth
- prevention and control of nausea and vomiting after surgery
- along with meperidine (demerol) or other pain medicines
- sedation, relief of anxiety, and production of light sleep from which the patient can be easily aroused
- treatment and prevention of motion sickness

#### Who Should Not Use Promethazine HCl Tablets?

Promethazine should not be given to:

- children under two years of age
- patients who are unconscious
- patients who are allergic to promethazine, any of the ingredients in promethazine, or to other phenothiazines
- patients with lung symptoms including asthma
- children who are vomiting unless the vomiting is prolonged and there is a known cause

#### What Are The Risks?

***The following are the major potential risks and side effects of promethazine HCl tablets therapy. However, this list is not complete.***

- **Severe drowsiness and reduced mental alertness.** Promethazine HCl tablets may cause drowsiness which may impair your ability to ride a bike, drive a car, or operate machinery. This may be worsened if taken with alcohol or other drugs that also cause central nervous system (CNS) slowing such as sedatives, pain medicines, tranquilizers or certain drugs for depression.
- **Serious breathing problems.** Promethazine HCl tablets should not be used in patients with poor lung function such as chronic obstructive lung disease or breathing problems while sleeping (sleep apnea).
- **Increased risk of seizures.** Promethazine HCl tablets should be used with caution in patients with seizures or who are on other medicines which may also increase the risk of seizures.
- **Bone-marrow problems and blood cell production.** Promethazine HCl tablets should not be used in patients with



bone-marrow problems or used with other drugs that affect the bone marrow's production of blood cells.

- **Neuroleptic malignant syndrome.** This potentially deadly syndrome includes symptoms such as fever, muscle rigidity, mental changes, changes in pulse or blood pressure, fast heartbeat, increased sweating or irregular heart rhythm.
- **The most common side effects are** drowsiness, changes in blood pressure, skin reactions, blood cell changes and breathing problems. Increased excitability or abnormal movements may occur after one dose of promethazine. If they do, consult your doctor about using another medicine.

### What Should I Tell My Healthcare Professional?

Before you start taking promethazine HCl tablets, tell your healthcare professional if you:

- have narrow-angle glaucoma
- have an enlarged prostate
- have a stomach ulcer
- have an intestinal blockage
- have a bladder blockage
- have heart problems
- have liver problems
- have breathing or lung problems
- have sleep apnea (breathing problems when sleeping)
- have seizures
- drink alcohol
- are trying to become pregnant, are already pregnant, or are breast-feeding

### Can Other Medicines Or Food Affect Promethazine?

Promethazine HCl Tablets and certain other medicines can interact with each other. Tell your healthcare professional about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how promethazine works or promethazine may affect how your other medicines work. Know the medicines you take. Keep a list of them with you to show your healthcare professional.

Especially tell your healthcare professional if you take:

- medicines that affect your brain such as anti-anxiety medicine, sleeping pills, pain medicines, sedatives, narcotics, anti-depressants or tranquilizers
- epinephrine
- a monoamine oxidase inhibitor (MAOI) which is used to treat depression or other mental disorders
- medicines called anticholinergics

### Storage

Store at controlled room temperature 20° - 25°C (68° - 77°F). Dispense in tight, light-resistant container.

**Distributed by: Sun Pharmaceutical Industries, Inc.**  
Cranbury, NJ 08512

6044T04  
Rev. 07/2014

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- 12.5 mg 100 count**

**NDC 57664-107-88**

**Promethazine Hydrochloride Tablets, USP**

**12.5 mg**

**Rx Only**

**100 Tablets**

NDC 57664-107-88

# Promethazine Hydrochloride Tablets, USP

**12.5 mg**

Rx Only  
100 Tablets



Each tablet contains: Promethazine Hydrochloride, USP 12.5 mg

CONTAINS: FD&C Yellow No. 6

Usual Dosage: See package insert for complete dosage recommendations.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F). (See USP Controlled Room Temperature).

**KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

6051L04 Rev. 10/14

Mfg. and Dist. by: **Sun Pharmaceutical Industries, Inc.**  
Cranbury, NJ 08512



N 3 57664 10788 1

LOT NO.:  
EXP. DATE: | 1/2" Unvarnished Area

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- 25 mg 100 count

NDC 57664-108-88

Promethazine Hydrochloride Tablets, USP

25 mg

Rx Only


100 Tablets

NDC 57664-108-88

# Promethazine Hydrochloride Tablets, USP

**25 mg**

Rx Only  
100 Tablets



Each tablet contains: Promethazine Hydrochloride, USP 25 mg

Usual Dosage: See package insert for complete dosage recommendations.


Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F). (See USP Controlled Room Temperature).

**KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

6049L03 Rev. 10/14

Mfg. and Dist. by: **Sun Pharmaceutical Industries, Inc.**  
Cranbury, NJ 08512



N 3 57664 10888 8

LOT NO.:  
EXP. DATE: | 1/2" Unvarnished Area

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- 50 mg 100 count

NDC 57664-109-88

Promethazine Hydrochloride Tablets, USP

50 mg

Rx Only

100 Tablets

NDC 57664-109-88

# Promethazine Hydrochloride Tablets, USP

50 mg

Rx Only  
100 Tablets



**SUN**  
PHARMA

Each tablet contains: Promethazine Hydrochloride, USP 50 mg

Usual Dosage: See package insert for complete dosage recommendations.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F). (See USP Controlled Room Temperature).

**KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

6046L03      Rev. 10/14

Mfg. and Dist. by: **Sun Pharmaceutical Industries, Inc.**  
Cranbury, NJ 08512



N 3 57664 10988 5

LOT NO.:      1/2" Unvarnished Area

EXP. DATE:

**PROMETHAZINE HYDROCHLORIDE**

promethazine hydrochloride tablet

**Product Information**

Product Type

HUMAN PRESCRIPTION DRUG

Item Code (Source)

NDC:57664-107

Route of Administration

ORAL

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
PROMETHAZINE HYDROCHLORIDE (UNII: R61ZEH7111) (PROMETHAZINE - UNII: FF28EJQ494)	PROMETHAZINE HYDROCHLORIDE	12.5 mg

**Inactive Ingredients**

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q815X)	
MAGNESIUM STEARATE (UNII: 70097M6130)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

**Product Characteristics**

Color	pink (Light peach)	Score	2 pieces
Shape	ROUND (ROUND)	Size	8mm
Flavor		Imprint Code	107
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:57664-107-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
2	NDC:57664-107-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
3	NDC:57664-107-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
4	NDC:57664-107-13	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
5	NDC:57664-107-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040863	01/27/2009	

**PROMETHAZINE HYDROCHLORIDE**

promethazine hydrochloride tablet

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:57664-108
<b>Route of Administration</b>	ORAL		

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
PROMETHAZINE HYDROCHLORIDE (UNII: R61ZEH7111) (PROMETHAZINE - UNII:FF28EJQ494)	PROMETHAZINE HYDROCHLORIDE	25 mg

**Inactive Ingredients**

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

**Product Characteristics**

<b>Color</b>	white (White to off-white)	<b>Score</b>	2 pieces
<b>Shape</b>	ROUND (ROUND)	<b>Size</b>	8mm
<b>Flavor</b>		<b>Imprint Code</b>	108
<b>Contains</b>			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:57664-108-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
2	NDC:57664-108-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
3	NDC:57664-108-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
4	NDC:57664-108-13	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
5	NDC:57664-108-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040863	01/27/2009	

**PROMETHAZINE HYDROCHLORIDE**

promethazine hydrochloride tablet

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:57664-109	
<b>Route of Administration</b>	ORAL			
<b>Active Ingredient/Active Moiety</b>				
	<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>	
	PROMETHAZINE HYDROCHLORIDE (UNII: R61ZEH7111) (PROMETHAZINE - UNII:FF28EJQ494)	PROMETHAZINE HYDROCHLORIDE	50 mg	
<b>Inactive Ingredients</b>				
	<b>Ingredient Name</b>		<b>Strength</b>	
	HYPROMELLOSES (UNII: 3NXW29V3WO)			
	LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)			
	MAGNESIUM STEARATE (UNII: 70097M6130)			
	CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)			
	D&C RED NO. 27 (UNII: 2LRS18SU6K)			
	D&C RED NO. 30 (UNII: 2S42T2808B)			
<b>Product Characteristics</b>				
<b>Color</b>	pink (Light pink)	<b>Score</b>	no score	
<b>Shape</b>	ROUND (ROUND)	<b>Size</b>	10mm	
<b>Flavor</b>		<b>Imprint Code</b>	109	
<b>Contains</b>				
<b>Packaging</b>				
<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:57664-109-83	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
2	NDC:57664-109-88	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
3	NDC:57664-109-08	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
4	NDC:57664-109-13	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
5	NDC:57664-109-18	1000 in 1 BOTTLE; Type 0: Not a Combination Product	12/03/2010	
<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>	
ANDA	ANDA040863	01/27/2009		

**Labeler** - Sun Pharmaceutical Industries, Inc. (146974886)

**Registrant** - Sun Pharmaceutical Industries, Inc. (146974886)

### Establishment

Name	Address	ID/FEI	Business Operations
Sun Pharmaceutical Industries, Inc		146974886	analysis(57664-107, 57664-108, 57664-109) , manufacture(57664-107, 57664-108, 57664-109) , pack(57664-107, 57664-108, 57664-109)

Revised: 12/2017

Sun Pharmaceutical Industries, Inc.