HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARTEMIS® XR safely and effectively. See full prescribing information for XARTEMIS XR.

XARTEMIS XR (oxycodone hydrochloride and acetaminophen) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1976

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); 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

See full prescribing information for complete boxed warning.

- **XARTEMIS XR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addication, abuse and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)**
- **Accidental Ingestion of XARTEMIS XR, especially in children, can result in fatal overdose of oxycodone. (5.3)**
- **Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)**
- **XARTEMIS XR contains acetaminophen. 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. (5.6, 5.13)**
- **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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/2018
Warnings and Precautions (5.2)	09/2018

----------INDICATIONS AND USAGE----------

XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use:
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

---------- DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- The recommended dose of XARTEMIS XR is 2 tablets every 12 hours without regard to food. (2.2)
- Instruct patients to swallow XARTEMIS XR tablets intake and not to break, chew, crush, cut, dissolve or split, the tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time with enough water to ensure complete swallowing immediately after placing in mouth. (2.1)
- Do not abruptly discontinue XARTEMIS XR in a physically-dependent patient. (2.6)
- Patients with Hepatic Impairment and Renal Impairment: Start with one tablet every 12 hours and monitor closely for respiratory depression. (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release tablets (oxycodone hydrochloride/acetaminophen): 7.5 mg/325 mg (3)

---------- CONTRAINDICATIONS ----------

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Hypersensitivity to oxycodone, acetaminophen. (4)

----------WARNINGS AND PRECAUTIONS ----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Use with caution in patients at increased risk of hypotension and in patients in circulatory shock. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of XARTEMIS XR in patients with impaired consciousness or coma. (5.12)

----------ADVERSE REACTIONS----------

The most common adverse events with XARTEMIS XR are nausea, dizziness, headache, vomiting, constipation and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue XARTEMIS XR if serotonin syndrome is suspected. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of oxycodone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with XARTEMIS XR because they may reduce analgesic effect of XARTEMIS XR or precipitate withdrawal symptoms. (5.17, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not Recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: September 2018

FULL PRESCRIBING INFORMATION: CONTENTS

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); 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

XARTEMIS XR exposes 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 XARTEMIS XR, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMIS XR. Monitor for respiratory depression, especially during initiation of XARTEMIS XR or following a dose increase. Instruct patients to swallow XARTEMIS XR tablets whole; crushing, chewing, or dissolving XARTEMIS XR can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of XARTEMIS XR, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized 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 and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of XARTEMIS XR with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone 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 oxycodone plasma concentration. Monitor patients receiving XARTEMIS XR and any CYP3A4 inhibitor or *inducer [see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Hepatotoxicity

XARTEMIS XR contains acetaminophen. 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 and Precautions (5.6, 5.13)]*.

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 and Precautions (5.7), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of XARTEMIS XR 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.**

1 INDICATIONS AND USAGE

XARTEMIS XR is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve XARTEMIS XR 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

XARTEMIS XR is not interchangeable with other oxycodone/acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- 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 and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with XARTEMIS XR and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

XARTEMIS XR is given orally. Instruct patients to swallow XARTEMIS XR tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in mouth *[see Patient Counseling Information (17)]*. Do not break, chew, crush, cut, dissolve or split the tablets. Breaking, chewing, crushing, cutting, dissolving or splitting XARTEMIS XR tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

The total daily dose of acetaminophen from all drug products should not exceed 4,000 milligrams.

2.2 Initial Dosage

Use of XARTEMIS XR as the First Opioid Analgesic

The recommended dosage of XARTEMIS XR is 2 tablets every 12 hours administered with or without food. The second dose of 2 tablets may be administered as early as 8 hours after the initial dose if patients require analgesia at that time. Subsequent doses are to be administered 2 tablets every 12 hours.

2.3 Dosage Modifications in Patients with Hepatic Impairment

In patients with hepatic impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression, sedation, and hypotension *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.4 Dosage Modifications in Patients with Renal Impairment

In patients with renal impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression, sedation, and hypotension *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin XARTEMIS XR, start with one tablet every 12 hours, consider using a lower dosage of the concomitant CNS depressant, and monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

2.6 Discontinuation of XARTEMIS XR

When a patient who has been taking XARTEMIS XR regularly and may be physically dependent no longer requires therapy with XARTEMIS XR, 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 XARTEMIS XR in a physically-dependent patient *[see Warnings and Precautions (5), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XARTEMIS XR is an extended-release tablet for oral administration. Each tablet contains 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen.

4 CONTRAINDICATIONS

XARTEMIS XR tablets are contraindicated in patients with

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)]*
- Hypersensitivity to oxycodone or acetaminophen (e.g., anaphylaxis) *[see Warnings and Precautions (5.13)], Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

XARTEMIS XR contains oxycodone, a Schedule II controlled substance. As an opioid, XARTEMIS XR exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed XARTEMIS XR. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing XARTEMIS XR, and monitor all patients receiving XARTEMIS XR 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 addiction or abuse) 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 XARTEMIS XR, but use in such patients necessitates intensive counseling about the risks and proper use of XARTEMIS XR 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 XARTEMIS XR. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity *[see Patient Counseling Information (17)]*. 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.

Abuse or misuse of XARTEMIS XR by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the oxycodone and can result in overdose and death *[see Overdosage (10)]*.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 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 from opioid use, 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 (10)]*. Carbon dioxide (CO_2) 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 XARTEMIS XR, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially during the first 24 to 72 hours of initiating therapy with XARTEMIS XR and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of XARTEMIS XR are essential *[see Dosage and Administration (2)]*. Overestimating the XARTEMIS XR dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of XARTEMIS XR, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of XARTEMIS XR 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 Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

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

Concomitant use of XARTEMIS XR 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 oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.3)]*, particularly when an inhibitor is added after a stable dose of XARTEMIS XR is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in XARTEMIS XR-treated patients may increase oxycodone plasma concentrations and prolong adverse reactions. When using XARTEMIS XR with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in XARTEMIS XR-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of XARTEMIS XR until stable drug effects are achieved *[see Dosage and Administration (2), Drug Interactions (7)]*.

Concomitant use of XARTEMIS XR with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using XARTEMIS XR with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.6 Hepatotoxicity

XARTEMIS XR contains oxycodone and acetaminophen. 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 typical daily acetaminophen contribution from XARTEMIS XR is 1,300 mg.

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.

5.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of XARTEMIS XR 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 Drug Interactions (7)]*.

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 XARTEMIS XR is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate dangerous 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 Drug Interactions (7) and Patient Counseling Information (17)]*.

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

The use of XARTEMIS XR 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: XARTEMIS XR-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 XARTEMIS XR *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating XARTEMIS XR and when XARTEMIS XR is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 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.

5.10 Severe Hypotension

XARTEMIS XR may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an 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 Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or triturating the dosage of XARTEMIS XR. In patients with circulatory shock, XARTEMIS XR may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of XARTEMIS XR in patients with circulatory shock.

5.11 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. Inform patients about the signs of serious skin reactions, and discontinue use at the first appearance of skin rash or any other sign of hypersensitivity.

5.12 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_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), XARTEMIS XR may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with XARTEMIS XR.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of XARTEMIS XR in patients with impaired consciousness or coma.

5.13 Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with 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 XARTEMIS XR immediately and seek medical care if they experience these symptoms. Do not prescribe XARTEMIS XR for patients with acetaminophen allergy.

5.14 Difficulty Swallowing

Due to characteristics of the formulation that cause the tablets to swell and become sticky when wet, consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen. Instruct patients not to pre-soak, lick or otherwise wet XARTEMIS XR tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in mouth.

5.15 Risks of Use in Patients with Gastrointestinal Conditions

XARTEMIS XR is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in XARTEMIS XR 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.

5.16 Increased Risk of Seizures in Patients with Seizure Disorder

The oxycodone in XARTEMIS XR 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. Monitor patients with a history of seizure disorders for worsened seizure control during XARTEMIS XR therapy.

5.17 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 XARTEMIS XR. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing XARTEMIS XR, gradually taper the dosage *[see Dosage and Administration (2)]*. Do not abruptly discontinue XARTEMIS XR *[see Drug Abuse and Dependence (9.3)]*.

5.18 Driving and Operating Machinery

XARTEMIS XR may impair the mental and/or physical abilities required 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 XARTEMIS XR and know how they will react to the medication *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.9)]*
- Severe Hypotension *[see Warnings and Precautions (5.10)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.15)]*
- Seizures *[see Warnings and Precautions (5.16)]*
- Withdrawal *[see Warnings and Precautions (5.17)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In safety data from two Phase 3 (one placebo-controlled, one open-label) trials where multiple doses of XARTEMIS XR were administered for up to 42 days, the most common adverse reactions (reported by ≥10% in any XARTEMIS XR dose group) were: nausea, dizziness and vomiting. The most common reasons for discontinuation due to AEs in these 2 studies (reported by ≥1% in any XARTEMIS XR dose group) were vomiting (4.8%) and nausea (4.1%); there were no reports of these adverse reactions in the placebo-treated patients.

A total of 1028 subjects in 14 clinical studies were treated with XARTEMIS XR during the clinical development program, including 892 subjects treated with 15 mg oxycodone and 650 mg acetaminophen. This dosage regimen of XARTEMIS XR was administered to 607 patients in two Phase 3 studies (one placebo-controlled and one open-label).

In a placebo-controlled post-bunionectomy acute pain trial, 329 patients were dosed with 15 mg oxycodone and 650 mg acetaminophen XARTEMIS XR or placebo orally every 12 hours, for approximately 48 hours (blinded period) *[see Clinical Studies (14)]*. **Table 1** lists the adverse reactions reported by ≥1% of XARTEMIS XR-treated patients and more frequently in XARTEMIS XR-treated patients compared with placebo.

Table 1. Treatment-Emergent Adverse Reactions* Reported by ≥1% of XARTEMIS XR-Treated Patients and More Frequently than Placebo in XARTEMIS XR-Treated Patients with Postoperative Bunionectomy Pain (blinded period)

Preferred Term	XARTEMIS XR (N = 166) %	Placebo (N = 163) %
Nausea	31	6
Dizziness	13	1
Headache	10	5
Vomiting	9	0
Constipation	4	3
Somnolence	4	<1
Rash	2	1
Blister	1	<1
Dysuria	1	0
Edema peripheral	1	0
Erythema	1	0
Excoriation	1	0
Hot flush	1	<1
Pruritus generalized	1	0

*A treatment-emergent adverse reaction refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Other Adverse Reactions Observed During the Premarketing Evaluation of XARTEMIS XR

The following adverse drug reactions not listed above occurred in ≥1% of XARTEMIS XR-treated patients in the pooled safety data from two Phase 3 studies (including a placebo-controlled and an open-label non-controlled safety study) where multiple-doses of XARTEMIS XR were administered every 12 hours for up to 42 days:

Gastrointestinal disorders: dry mouth, dyspepsia, diarrhea

General disorders and administration site conditions: fatigue

Investigations: hepatic enzyme increased

Psychiatric disorders: insomnia

Respiratory, thoracic and mediastinal disorders: cough

The following adverse drug reactions occurred in <1% of XARTEMIS XR-treated patients in the pooled safety data from the two Phase 3 studies described above:

Cardiac disorders: palpitations

Eye and ear disorders: tinnitus, vision blurred

Gastrointestinal disorders: abdominal discomfort, abdominal pain, esophageal spasm

General disorders and administration site conditions: asthenia, chest discomfort, chills, contusion, fall, feeling jittery, malaise, non-cardiac chest pain, thirst

Immune system disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood lactate dehydrogenase increased, blood pressure increased, gamma-glutamyltransferase increased, liver functional test abnormal

Metabolic and nutritional: decreased appetite

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal stiffness

Nervous system disorders: cognitive disorder, memory impairment, migraine, myoclonus, paraesthesia, sedation, tremor

Psychiatric disorders: anxiety, confusional state, disorientation, euphoric mood, mood altered, sleep disorder, withdrawal syndrome

Renal and urinary disorders: urine flow decreased

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups, hypopnea, oropharyngeal pain, throat irritation

Skin and subcutaneous tissue disorders: dermatitis, ecchymosis, hyperhidrosis, urticaria

Vascular disorders: flushing, hypertension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of XARTEMIS XR. 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.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs *[see Drug Interactions (7)]*.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use *[see Warnings and Precautions (5.9)]*.

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in XARTEMIS XR *[see Contraindications (4)]*.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with XARTEMIS XR.

Table 2: Clinically Significant Drug Interactions with XARTEMIS XR

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of XARTEMIS XR and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of XARTEMIS XR and CYP2D6 and CYP3A4 inhibitors,

	particularly when an inhibitor is added after a stable dose of XARTEMIS XR is achieved *[see Warnings and Precautions (5.5)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to XARTEMIS XR.
Intervention:	If concomitant use is necessary, consider dosage reduction of XARTEMIS XR until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the XARTEMIS XR dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of XARTEMIS XR and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.4)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the XARTEMIS XR dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider XARTEMIS XR dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	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 Dosage and Administration (2.5), Warnings and Precautions (5.7)]*.

Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Adverse Reactions (6.2)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue XARTEMIS XR if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*. 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.
Intervention:	The use of XARTEMIS XR is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of XARTEMIS XR and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of XARTEMIS XR and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when XARTEMIS XR is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. Available data with XARTEMIS XR are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

There are no adequate and well-controlled studies of XARTEMIS XR tablets or oxycodone/acetaminophen in pregnant women. Epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. The incidence of malformations in human pregnancies has not been established for oxycodone as the data are limited.

No animal reproductive or developmental studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.

Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, a reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation.

Animal reproduction studies with oral administrations of oxycodone HCl in in rats and rabbits during the period of organogenesis at doses 2.6 and 8.1 times, respectively, the human dose of 60 mg/day did not reveal evidence of teratogenicity or embryo-fetal toxicity. In several published studies,

treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged maternal 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 and 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 and signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

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. XARTEMIS XR is not recommended for use in women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including XARTEMIS XR, 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.

Data

Human Data

Two large population based studies have evaluated the safety of acetaminophen in pregnant women during the first trimester; neither study showed an increased risk of congenital malformations. Available published data on oxycodone exposure during pregnancy and risk for malformations are limited and do not allow conclusions regarding a possible association.

Animal Data

No reproductive or developmental studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no

evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2 times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3 times the MHDD, based on a body surface area comparison. In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 2.6 and 8.1 times an adult human dose of 60 mg/day, respectively, on a mg/m^2 basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects including altered stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human dose of 60 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended-release oxycodone, including XARTEMIS XR, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with XARTEMIS XR.

Acetaminophen is present in human milk in small quantities. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 to 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use.

Clinical Considerations

Monitor infants exposed to XARTEMIS XR through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

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 (6.2)]*.

8.4 Pediatric Use

Safety and effectiveness of XARTEMIS XR in pediatric patients under the age of 18 years have not been established. The use of XARTEMIS XR in the pediatric population is not recommended.

8.5 Geriatric Use

Of the 607 subjects in the Phase 3 studies treated with XARTEMIS XR, 63 (10.3%) were older than age 65, of which 10 (1.6%) were older than age 75. No untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride/acetaminophen extended-release tablets. However, special precaution should be given when determining the dosing amount and frequency of XARTEMIS XR for geriatric patients, since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients.

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 XARTEMIS XR slowly in geriatric patients and monitor closely for signs of respiratory depression *[see Warnings and Precautions (5.8)]*.

Oxycodone 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.

8.6 Hepatic Impairment

XARTEMIS XR contains oxycodone and acetaminophen, which are extensively metabolized in the liver. Their clearance may be decreased in patients with hepatic impairment. In patients with hepatic impairment a dosage adjustment is recommended *[see Dosage and Administration (2.3)]*. Monitor closely for respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Information from oxycodone HCl indicates that patients with renal impairment had higher plasma concentrations of oxycodone than subjects with normal renal function. In patients with renal impairment, a dosage adjustment is recommended *[see Dosage and Administration (2.4)]*. Monitor closely for respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XARTEMIS XR contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

XARTEMIS XR contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. XARTEMIS XR can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

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. Healthcare 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.

XARTEMIS XR, 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 the Abuse of XARTEMIS XR

XARTEMIS XR is for oral use only. Abuse of XARTEMIS XR poses a risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing, or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk of overdose and death is increased with concurrent abuse of alcohol or other central nervous system depressants.

With intravenous abuse, the inactive ingredients in XARTEMIS XR can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

9.3 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 dose 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.

XARTEMIS XR should not be abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2)]*. If XARTEMIS XR is 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 symptoms *[see Use in Specific Populations (8.1, 8.2)]*.

10 OVERDOSAGE

Clinical Presentation
Following an acute overdosage, toxicity may result from the oxycodone or the acetaminophen.

Oxycodone
Acute overdosage with XARTEMIS XR is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Acetaminophen
In acetaminophen overdosage, dose-dependent potentially fatal hepatic necrosis is the most serious adverse effect. 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
A single or multiple drug overdose with oxycodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate

treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, assisted ventilation, and other supportive measures should be employed as indicated.

Oxycodone
In case of overdose, priorities are the reestablishment 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 oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of oxycodone in XARTEMIS XR, 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 usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome 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 begun with care and by titration with smaller than usual doses of the antagonist.

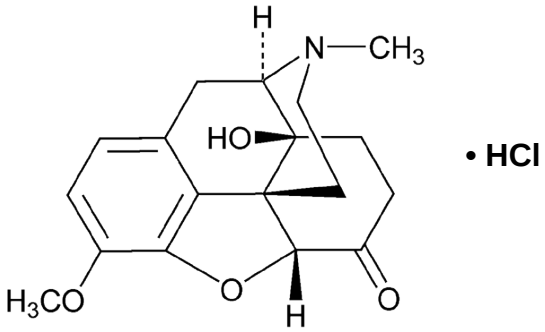
Acetaminophen
Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained 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.

11 DESCRIPTION

XARTEMIS XR (oxycodone hydrochloride and acetaminophen) extended-release tablets combine two analgesics, oxycodone hydrochloride 7.5 mg and acetaminophen 325 mg for oral administration.

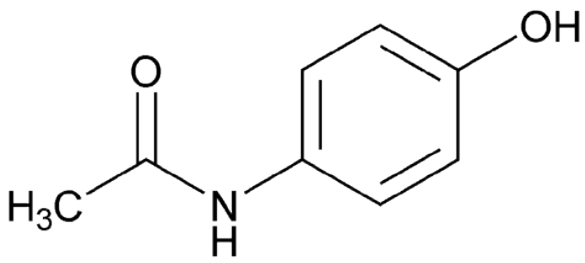
Oxycodone hydrochloride, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride, is an opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine. The structural formula for oxycodone hydrochloride is as follows:



• HCl

$C_{18}H_{21}NO_4$ • HCl **MW = 351.82**

Acetaminophen, 4'-hydroxyacetanilide, is a white, odorless, crystalline powder, possessing a slightly bitter taste. The structural formula for acetaminophen is as follows:



$C_8H_9NO_2$ **MW = 151.16**

XARTEMIS XR is an extended-release tablet for oral administration containing both immediate- and extended-release components. XARTEMIS XR is formulated to immediately release a portion of its oxycodone and acetaminophen doses. XARTEMIS XR is designed to swell in gastric fluid and gradually release the remainder of oxycodone and acetaminophen to the upper gastrointestinal (GI) tract.

XARTEMIS XR also contains the following inactive ingredients: polyethylene oxide (Polyox), microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, polyvinyl alcohol, magnesium stearate, titanium dioxide, polyethylene glycol, colloidal silicon dioxide, talc, pregelatinized starch, FD&C Blue #2 aluminum lake, citric acid anhydrous powder, and edetate disodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with oxycodone. 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.

Acetaminophen is a non-opioid, non-salicylate analgesic, and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined. The antipyretic effect of acetaminophen is accomplished through the inhibition of endogenous pyrogen action on the hypothalamic heat-regulating centers.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brainstem 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.

Oxycodone 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 with hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by oxycodone HCl. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone causes a reduction in motility 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

Oxycodone 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 (6)]*. 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 low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical 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 (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. 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 (active moiety) 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 (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing oxycodone 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 (2.1, 2.2, 2.4)]*.

The dose of XARTEMIS XR must be individualized because the effective analgesic dose for some patients will be too high to be tolerated by other patients *[see Dosage and Administration (2.1)]*.

12.3 Pharmacokinetics

XARTEMIS XR is an extended-release bilayer formulation of oxycodone and acetaminophen (immediate- and extended-release layers) which is not interchangeable with other oxycodone/acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration. The activity of oxycodone hydrochloride is primarily due to the parent drug oxycodone.

Absorption
The oral bioavailability of oxycodone is 60 to 87%. Bioavailability (dose-normalized AUC and C_{max}) of oxycodone and acetaminophen following single- and multiple-doses of XARTEMIS XR tablets is comparable to immediate-release products containing oxycodone or acetaminophen.

Oxycodone plasma concentrations from this bilayer product are detectable within 30 minutes and reach a maximum concentration (C_{max}) in 3 to 4 hours after XARTEMIS XR administration. Maximum plasma concentrations of acetaminophen occur in 0.75 to 1 hour after XARTEMIS XR administration.

Steady-state plasma concentrations of oxycodone and acetaminophen are achieved within 24 hours of initiation of dosing of XARTEMIS XR (prior to the third dose of two XARTEMIS XR tablets administered every 12 hours). XARTEMIS XR produces steady-state maximum plasma concentrations of oxycodone that are greater than those following the first dose, while concentrations of acetaminophen are comparable to the first dose (**Table 2**).

Table 2. Mean (SD) Pharmacokinetics of XARTEMIS XR (two 7.5 mg oxycodone and 325 mg acetaminophen extended-release tablets; after a single dose and multiple doses every 12 hours for 4.5 days)

	Oxycodone		**Acetaminophen**	
	Single Dose (N=24)	Multiple Dose* (N=24)	Single Dose (N=24)	Multiple Dose* (N=24)
$AUC_{0\text{-}12h}$ (ng•h/mL)	136 (24)	208 (45)	24924 (5667)	28160 (5807)
C_{max} (ng/mL)	16.0 (3.6)	24.0 (5.4)	4858 (1066)	4793 (1132)
C_{min} (ng/mL)	6.9 (2.0)	9.3 (2.4)	738 (227)	853 (273)
Fluctuation (%)†	NA	83.9 (17.6)	NA	169.1 (39.8)
T_{max} (h)‡	3.0	3.0	1.0	1.0
$t_{1/2}$ (h)	NA	5.4 (0.9)	NA	6.9 (1.8)

*Steady-state results on Day 5 (0-12 hours)
† Fluctuation = $100•(C_{max}-C_{min})/C_{avg}$
‡ Median reported for T_{max}
NA = not applicable

Food Effect
When administered with a high- or low-fat meal, median T_{max} values of oxycodone were delayed by 2 hours and 1 hour, respectively. Mean AUC values are increased by 15 to 16% and peak concentrations are 12 to 25% higher for oxycodone. Food delayed median acetaminophen T_{max} by 1.5 hours. There is no change in mean acetaminophen AUC values and peak concentrations are 23 to 24% lower with food. XARTEMIS XR may be administered with or without food.

Distribution
Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone was approximately 45% bound to plasma protein at 37°C and a pH of 7.4. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.2)]*.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Elimination
Metabolism
Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;
b) conjugation with sulfate; and
c) 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.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Excretion

Oxycodone and its metabolites are eliminated primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; and conjugated oxymorphone ≤14%. Both free and conjugated noroxycodone have been found in urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life (mean ± SD) of oxycodone following administration of XARTEMIS XR was 4.5 ± 0.6 hours as compared to 3.9 ± 0.3 hours for immediate-release oxycodone.

Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in urine. Following administration of XARTEMIS XR, the apparent elimination half-life is 5.8 ± 2.1 hours as compared to 4.1 ± 1.1 hours for immediate-release acetaminophen.

Special Populations

Age: Geriatric Population

Population pharmacokinetic studies indicate that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65. A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of acetaminophen in elderly patients with normal renal and hepatic function.

Sex

Population pharmacokinetic analyses performed in a clinical study support the lack of gender effect on the pharmacokinetics of oxycodone.

Hepatic Impairment
The pharmacokinetics of XARTEMIS XR in patients with impaired hepatic function has not been studied. Oxycodone and acetaminophen are extensively metabolized, resulting in decreased clearance in patients with hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment
The pharmacokinetics of XARTEMIS XR in patients with renal impairment has not been studied. Patients with renal impairment have higher plasma concentrations of oxycodone than subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies were conducted with the combination of oxycodone and acetaminophen, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted. Long-term animal studies to evaluate the carcinogenic potential of acetaminophen have been completed by the National Toxicology Program. 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, on a body surface area comparison.

Mutagenesis
Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay *(Salmonella typhimurium* and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges and chromosomal aberrations in *in vitro* assays using Chinese hamster ovary cells. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 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
Studies in animals to evaluate the potential impact of oxycodone on fertility have not been conducted.

In studies of acetaminophen conducted by the National Toxicology Program, fertility assessments 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 1.7 times the MHDD (based on a body surface area 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 area 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.

14 CLINICAL STUDIES

Post-Operative Bunionectomy Pain Study

Efficacy was demonstrated in one multicenter, randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose clinical trial comparing XARTEMIS XR and placebo in patients with acute pain following a unilateral first metatarsal bunionectomy. A total of 303 patients with a mean age of 43 (range 18 to 73) years, meeting criteria for randomization (pain intensity ≥4 on a 0 to 10 numerical pain rating scale) and receiving a fixed-dose of 2 tablets of XARTEMIS XR 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen tablets or placebo every 12 hours over 48 hours were randomized. There were 36 early discontinuations (9% from XARTEMIS XR, 13% from placebo). Ibuprofen 400 mg every 4 hours as needed was allowed as rescue medication.

Mean baseline pain intensity scores were 6.2 in the XARTEMIS XR group (range: 4 to 10) and 6.0 in the placebo group (range: 1 to 10). Approximately 85% of the 150 subjects treated with XARTEMIS XR and 98% of the 153 subjects treated with placebo took rescue medication at least once for pain management during the 48 hours after the first dose. Median rescue medication use was 2 doses for XARTEMIS XR-treated subjects and 4 doses for placebo-treated subjects over the 48 hours; rescue medication was used by less than 50% of the XARTEMIS XR-treated patients after the first dose interval. Pain intensity was recorded at 2, 4, 8, and 12 hours after each dose, with additional recordings at 15, 30, 45, 60, and 90 minutes after the first dose. The median time to onset of pain relief was less than one hour for XARTEMIS XR. The primary endpoint was the summed pain intensity difference (change in pain from baseline) over 48 hours ($SPID_{48}$), which demonstrated improvement in pain from baseline for the XARTEMIS XR treatment group compared to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

XARTEMIS XR (oxycodone hydrochloride and acetaminophen) extended-release tablets are oval shaped tablets with a blue coating, debossed with “M” in a box over “115” on one side of the tablet. Each tablet contains 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen and is packaged in bottles and blister packs.

Bottles of 100	NDC 23635-115-01
Unit dose (10 x 10)	NDC 23635-115-62

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Important Administration Instructions
Instruct patients how to properly take XARTEMIS XR, including the following:

- XARTEMIS XR is not interchangeable with other forms of oxycodone/acetaminophen.
- XARTEMIS XR is a narcotic pain reliever and must be taken only as directed.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth, and not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth.
- Swallow each XARTEMIS XR tablet whole. Do not crush or dissolve. Do not use XARTEMIS XR for administration via nasogastric, gastric, or other feeding tubes as it may cause obstruction of feeding tubes.
- If they miss a dose to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next dose at the regularly scheduled time. Do not take more than 2 tablets at once unless instructed by their healthcare provider. If they are not sure about their dosing, call their healthcare provider.
- Do not adjust the dose of XARTEMIS XR without consulting with a physician or other healthcare provider.
- Do not take more than 4,000 milligrams of acetaminophen per day and to call their healthcare provider if they took more than the recommended dose.
- If physically dependent, do not to discontinue XARTEMIS XR without first discussing the need for a tapering regimen with a physician or other healthcare provider.

Addiction, Abuse, and Misuse
Inform patients that the use of XARTEMIS XR, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share XARTEMIS XR with others and to take steps to protect XARTEMIS XR 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 XARTEMIS XR or when the dose is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. 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 and Precautions (5.3)]*. Instruct patients to take steps to store XARTEMIS XR securely and to dispose of unused XARTEMIS XR by flushing the tablets down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if XARTEMIS XR is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids 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 physicians if they are taking, or plan to take serotonergic medications *[see Adverse Reactions (6.2), Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking XARTEMIS XR while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Oxycodone Hydrochloride Oral Solution *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids 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 and Precautions (5.9), Adverse Reactions (6.2)]*.

Hypotension

Inform patients that XARTEMIS XR 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 and Precautions (5.10)]*.

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in XARTEMIS XR. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6.2)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that XARTEMIS XR can cause fetal harm, and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients that breastfeeding is not recommended during treatment with XARTEMIS XR *[see Use in Specific Populations (8.2)]*.

Driving or Operating Machinery
Inform patients that XARTEMIS XR may impair the ability to perform potentially hazardous activities such as driving a car or operating dangerous machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.18)]*.

Use During Pregnancy
Instruct females of reproductive potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with XARTEMIS XR. Advise patients that safe use in pregnancy has not been established.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused XARTEMIS XR
Advise patients to flush the unused tablets down the toilet when XARTEMIS XR is no longer needed.

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Manufactured for:
Mallinckrodt Brand Pharmaceuticals, Inc.
Hazelwood, MO 63042 USA

Medication Guide

XARTEMIS® XR (ZAR-tem-iss) **(oxycodone hydrochloride and acetaminophen) Extended-Release Tablets, CII**

XARTEMIS XR is:

- A strong prescription pain medicine that contains an opioid (narcotic) and the medicine acetaminophen. XARTEMIS XR is used to treat certain types of short term (acute) pain when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) 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.

Important information about XARTEMIS XR:

- **Get emergency help right away if you take too much XARTEMIS XR (overdose).** When you first start taking XARTEMIS XR, 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.
- Taking XARTEMIS XR 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.
- Never give anyone else your XARTEMIS XR. They could die from taking it. Store XARTEMIS XR away from children and in a safe place to prevent stealing or abuse. Selling or giving away XARTEMIS XR is against the law.
- Get emergency help right away if you take more than 4,000 mg of acetaminophen in 1 day. Taking XARTEMIS XR with other products that contain acetaminophen can lead to serious liver problems and death.

Do not take XARTEMIS XR if you have:

- severe asthma, trouble breathing, or other lung problems.
- allergy to acetaminophen or oxycodone.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking XARTEMIS XR, 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 during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with XARTEMIS XR. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking XARTEMIS XR with certain other medicines can cause serious side effects that could lead to death.

When taking XARTEMIS XR:

- Do not change your dose. Take XARTEMIS XR exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours, at the same time every day. If you miss a dose, take XARTEMIS XR as soon as possible, then take your next dose 12 hours later. If it is almost time for your next dose, skip the missed dose. Take your next dose at the regular time. Do not take more than your prescribed daily dose in 24 hours.
- Swallow XARTEMIS XR whole. Do not cut, break, chew, crush, dissolve, snort or inject XARTEMIS XR because this may cause you to overdose and die. You should not receive XARTEMIS XR through a nasogastric tube or gastric tube (stomach tube).
- Take XARTEMIS XR 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth. Take each XARTEMIS XR tablet with enough water to be sure that you swallow it completely as soon as you place it in your mouth. Do not take more than your prescribed dose. If you miss a dose, take our next dose at your usual time.
- **Call your healthcare provider if XARTEMIS XR does not control your pain.**
- **If you have been taking XARTEMIS XR for more than a few days, do not stop taking it without talking to your healthcare provider.**
- After you stop taking XARTEMIS XR, flush any unused tablets down the toilet.

While taking XARTEMIS XR:

- Do not drive or operate heavy machinery, until you know how XARTEMIS XR affects you. XARTEMIS XR can make you sleepy, dizzy, or lightheaded.
- Do not drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with XARTEMIS XR may cause you to overdose and die.
- Do not take other products that contain acetaminophen while taking XARTEMIS XR.

The possible side effects of XARTEMIS XR are:

- 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.
- rash with hives, sores in your mouth or eyes, or your skin blisters and peels.

These are not all the possible side effects of XARTEMIS XR. 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**

Distributed by: Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO 63042 USA, www.Mallinckrodt.com or call 1-800-778-7898

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