Rx and OTC medications containing acetaminophen

The maximum total daily dose of acetaminophen administered by any route should not be exceeded. To minimize the potential risk of overdose, HCPs should discuss with their patients the use and amounts of acetaminophen contained in both prescription and OTC medications.

This list is designed to serve as a guide and is not meant to be a comprehensive directory of all available acetaminophen-containing products. It is important to carefully review any product's list of ingredients to determine whether and how much acetaminophen is contained within. Please refer to individual product labels for specific dosing guidelines.

Prescription intravenous product containing acetaminophen

OFIRMEV® (acetaminophen) injection

Prescription oral products containing acetaminophen (examples)

Acetaminophen and Oxycodone Combinations

Endocet® | Percocet® | Primlev® | Roxicet™ | XARTEMIS™ XR

Acetaminophen and Hydrocodone Combinations

Lorcet® | Norco® | Vicodin® ES | Xodol®
Lortab® | Vicodin® | Vicodin® HP | Zamicet™

Acetaminophen and Butalbital Combinations

Bupap® | Tencon®

Acetaminophen, Butalbital, and Caffeine Combinations

Dolgic® Plus | Esgic® | Fioricet® | Zebutal®

Acetaminophen and Isometheptene Combinations

Nodolor®

Acetaminophen and Codeine Combinations

Capital® w/codeine | Fioricet® w/codeine | Tylenol® w/codeine #3, #4

Acetaminophen and Tramadol Combinations

Ultracet®

OTC products containing acetaminophen (examples)

Acetaminophen Single-Agent Products

Acephen™ Suppositories
Anacin® Tablets
Cetafen® (various products under this brand name)
Children's Silapap™ Elixir
Children's Tylenol® (various products under this brand name)
Ed-APAP™ Children's Solution
ElixSure® Children's Fever Reducer/Pain Reliever
FeverAll® Suppositories
Genapap™ (various products under this brand name)
Jr. Tylenol® Meltaways
Mapap® (various products under this brand name)
Nortemp® Children's Suspension
Q-Pap™ (various products under this brand name)
RapiMed®
Silapap™ (various products under this brand name)
Tylenol® 8 Hour
Tylenol® Arthritis Pain
Tylenol® Extra Strength (various products under this brand name)
Tylenol® Infants' Drops
Tylenol® Regular Strength
Valorin™ (various products under this brand name)

Acetaminophen Combination Products

Alka-Seltzer® (various products under this brand name)
Anacin® Advanced Headache Formula
Benadryl® (various products under this brand)
Co-APAP™ Cough Formula M Multi-Symptom
Comtrex® (various products under this brand name)
Contac® (various products under this brand name)
Coricidin® (various products under this brand name)
DayQuil® (various products under this brand name)
Dimetapp® (various products under this brand name)
Dristan® Cold
Excedrin® (various products under this brand name)
Goody's® Headache Powders (various products under this brand name)
Mapap® (various products under this brand name)
Midol® (various products under this brand name)
NyQuil® (various products under this brand name)
Robitussin® (various products under this brand name)
Sudafed® (various products under this brand name)
Theraflu® (various products under this brand name)
Triaminic® (various products under this brand name)
Tylenol® Cold (various products under this brand name)
Vanquish® Caplets
Vicks® Formula 44 (various products under this brand name)

INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid anagesics, and the reduction of fever.

IMPORTANT RISK INFORMATION

WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- **the dose in milligrams (mg) and milliliters (mL) is not confused;**
- **the dosing is based on weight for patients under 50 kg;**
- **infusion pumps are properly programmed; and**
- **the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.**

OFIRMEV 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 the recommended maximum daily limits, and often involve more than one acetaminophen-containing product.

INDICATIONS AND USAGE

XARTEMIS™ XR (oxycodone HCl and acetaminophen) Extended-Release Tablets (CII) is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse, misuse, overdose, and death 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.

IMPORTANT RISK INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and HEPATOTOXICITY

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 or conditions.

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.

Accidental Exposure

Accidental ingestion of XARTEMIS XR, especially in children, can result in a fatal overdose of oxycodone.

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.

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 the maximum daily limit, and often involve more than one acetaminophen-containing product.

Please see additional Important Risk Information, including boxed warnings, for OFIRMEV® and XARTEMIS™ XR and in accompanying Full Prescribing Information for each product.

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INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and reduction of fever.

IMPORTANT RISK INFORMATION

CONTRAINDICATIONS

- Acetaminophen is contraindicated in patients with:
  - known hypersensitivity to acetaminophen or to any of the excipients in the intravenous (IV) formulation.
  - severe hepatic impairment or severe active liver disease.

WARNINGS AND PRECAUTIONS

- Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death. Do not exceed the maximum recommended daily dose of acetaminophen. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products. Dosing errors could result in accidental overdose and death.
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min).
- 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.
- Hypersensitivity and anaphylaxis associated with the use of acetaminophen have been reported. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus.
- The antipyretic effects of OFIRMEV may mask fever.

ADVERSE REACTIONS

- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.
- Common adverse reactions in adults include nausea, vomiting, headache, and insomnia. Common adverse reactions in pediatric patients include nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Pregnancy Category C. OFIRMEV should be given to a pregnant woman only if clearly needed.
- Breast Feeding: While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration.
- Pediatrics: The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.

INDICATIONS AND USAGE

XARTEMIS™ XR (oxycodone HCl and acetaminophen) Extended-Release Tablets (CII) is used to treat pain that is not expected to last a long time but painful enough to need this type of medicine. XARTEMIS XR is an opioid (narcotic). It has risks of addiction, abuse, misuse, overdose, and death, even when taken at the dose your doctor prescribed. Because of this, XARTEMIS XR should be used only when other medicines don't work.

IMPORTANT RISK INFORMATION

CONTRAINDICATIONS

- XARTEMIS XR is contraindicated in patients with:
  - known hypersensitivity to oxycodone, acetaminophen, or any other component of this product.
  - significant respiratory depression.
  - acute or severe bronchial asthma or hypercarbia.
  - known or suspected paralytic ileus.

WARNINGS AND PRECAUTIONS

- XARTEMIS XR contains oxycodone, a Schedule II controlled substance. As an opioid, XARTEMIS XR exposes users to the risks of addiction, abuse, and misuse. 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. 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.
- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. 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 dose increase. 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. In patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression, XARTEMIS XR may decrease respiratory drive to the point of apnea.
- Hypotension, profound sedation, coma, respiratory depression, and death may result if XARTEMIS XR is used concomitantly with alcohol or other central nervous system (CNS) depressants.
- The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.
- 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.
- The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure.
- Oxycodone may cause severe hypotension particularly in individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs which compromise vasomotor tone such as phenothiazines.
- Due to the potential for acetaminophen hepatotoxicity at doses higher than 4000 milligrams/day, XARTEMIS XR should not be used concomitantly with other acetaminophen-containing products.
- Hypersensitivity and anaphylaxis associated with use of acetaminophen have been reported. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting.
- 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.
- Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Oxycodone may cause spasm of the Sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.
- Since the CYP3A4 isoenzyme plays a major role in the metabolism of XARTEMIS XR, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.
- XARTEMIS XR may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

ADVERSE REACTIONS

- Serious adverse events may include respiratory depression and hepatotoxicity.
- Common adverse events include nausea, dizziness, headache, vomiting, constipation and somnolence.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Prolonged use of XARTEMIS XR during pregnancy can result in withdrawal signs in the neonate, which can be life threatening.
- Breast feeding: Oxycodone is present in human milk and may result in accumulation and toxicities such as sedation and respiratory depression in some infants. Acetaminophen is present in human milk in small quantities.
- Pediatrics: Safety and effectiveness in pediatric patients under the age of 18 years have not been established.

Please see additional Important Risk Information regarding OFIRMEV® and XARTEMIS™ XR, including boxed warnings in accompanying Full Prescribing Information for each product.

OFIRMEV®
(acetaminophen) injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OFIRMEV (acetaminophen) Injection
Initial U.S. Approval: 1951

WARNING:
RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

See full prescribing information for complete boxed warning

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death.

OFIRMEV 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 the recommended maximum daily limits, and often involve more than one acetaminophen-containing product (5.1).

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

OFIRMEV (acetaminophen) injection is indicated for the

- Management of mild to moderate pain (1)
- Management of moderate to severe pain with adjunctive opioid analgesics (1)
- Reduction of fever (1)

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

- OFIRMEV may be given as a single or repeated dose. (2.1)
- OFIRMEV should be administered only as a 15-minute intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:

- 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:

- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:

- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

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

- Injection for intravenous infusion.
- Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). (3)

---------- **CONTRAINDICATIONS** ----------

Acetaminophen is contraindicated:

- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation. (4)
- In patients with severe hepatic impairment or severe active liver disease. (4)

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

- Administration of acetaminophen in doses higher than recommended (by all routes of administration and from all acetaminophen-containing products including combination products) may result in hepatic injury, including the risk of liver failure and death. (5.1)
- Do not exceed the maximum recommended daily dose of acetaminophen (by all routes of administration and all acetaminophen-containing products including combination products). (5.1)
- Take care when prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death. (5.3)
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤ 30 mL/min). (5.1)
- Discontinue OFIRMEV immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2, 5.4)

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients. (6.1)

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

---------- **DRUG INTERACTIONS** ----------

- Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. (7.1)
- Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. (7.2)

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

- Pregnancy: Category C. There are no studies of intravenous acetaminophen in pregnant women. Use only if clearly needed. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients less than 2 years of age. The safety and effectiveness of OFIRMEV in pediatric patients older than 2 years is supported by evidence from adequate and well controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)
- Hepatic Impairment: OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)
- Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: Risk of Medication Errors and Hepatotoxicity

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- **the dose in milligrams (mg) and milliliters (mL) is not confused;**
- **the dosing is based on weight for patients under 50 kg;**
- **infusion pumps are properly programmed; and**
- **the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.**

OFIRMEV 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 the maximum daily limits, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for

- the management of mild to moderate pain
- the management of moderate to severe pain with adjunctive opioid analgesics
- the reduction of fever.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents who weigh 50 kg and above. Calculated maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen. Exceeding the maximum mg/kg daily dose of acetaminophen as described in Tables 1 and 2 may result in hepatic injury, including the risk of liver failure and death. To avoid the risk of overdose, ensure that the total amount of acetaminophen from all routes and from all sources does not exceed the maximum recommended dose.

2.2 Recommended Dosage: Adults and Adolescents

Adults and adolescents weighing 50 kg and over: the recommended dosage of OFIRMEV is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Adults and adolescents weighing under 50 kg: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Table 1. Dosing for Adults and Adolescents

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

Table 2. Dosing for Children

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

2.4 Instructions for Intravenous Administration

For adult and adolescent patients weighing ≥ 50 kg requiring 1000 mg doses of OFIRMEV, administer the dose by inserting a vented intravenous set through the septum of the 100 mL vial. OFIRMEV may be administered without further dilution. Examine the vial contents before dose preparation or administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15-minutes. Use aseptic technique when preparing OFIRMEV for intravenous infusion. Do not add other medications to the OFIRMEV vial or infusion device.

For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV vial and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL vial of OFIRMEV is not intended for use in patients weighing less than 50 kg. OFIRMEV is a single-use vial and the unused portion must be discarded.

Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump.

Monitor the end of the infusion in order to prevent the possibility of an air embolism, especially in cases where the OFIRMEV infusion is the primary infusion.

Once the vacuum seal of the glass vial has been penetrated, or the contents transferred to another container, administer the dose of OFIRMEV within 6 hours.

Do not add other medications to the OFIRMEV solution. Diazepam and chlorpromazine hydrochloride are physically incompatible with OFIRMEV, therefore do not administer simultaneously.

3 DOSAGE FORMS AND STRENGTHS

OFIRMEV is a sterile, clear, colorless, non pyrogenic, preservative free, isotonic formulation of acetaminophen intended for intravenous infusion. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

4 CONTRAINDICATIONS

Acetaminophen is contraindicated:

- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death *[see Overdosage (10)]*. Do not exceed the maximum recommended daily dose of acetaminophen *[see Dosage and Administration (2)]*. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min) *[see Use in Specific Populations (8.6, 8.7)]*.

5.2 Serious Skin Reactions

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

5.3 Risk of Medication Errors

Take care when prescribing, preparing, and administering OFIRMEV (acetaminophen) Injection in order to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits *[see Dosage and Administration (2)]*.

5.4 Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.2)]*
- Allergy and Hypersensitivity *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

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

Adult Population

A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 3. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Table 3. Treatment-Emergent Adverse Reactions Occurring in ≥ 3% of OFIRMEV-treated Patients and at a greater frequency than Placebo in Placebo-Controlled, Repeated Dose Studies

System Organ Class – Preferred Term	OFIRMEV (N=402) n (%)	Placebo (N=379) n (%)
Gastrointestinal Disorders		
Nausea	138 (34)	119 (31)
Vomiting	62 (15)	42 (11)
General Disorders and Administration Site Conditions		
Pyrexia*	22 (5)	52 (14)
Nervous System Disorders		
Headache	39 (10)	33 (9)
Psychiatric Disorders		
Insomnia	30 (7)	21 (5)

* Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

Pediatric Population

A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=355) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, diarrhea

General disorders and administration site conditions: injection site pain, edema peripheral, pyrexia

Investigations: hepatic enzyme increase

Metabolism and nutrition disorders: hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia

Musculoskeletal and connective tissue disorders: muscle spasm, pain in extremity

Nervous system disorders: headache

Psychiatric disorders: insomnia

Renal and urinary disorders: oliguria

Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pleural effusion, stridor, wheezing

Skin and subcutaneous tissue disorders: periorbital edema, rash

Vascular disorders: hypertension, hypotension

7 DRUG INTERACTIONS

7.1 Effects of other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

7.2 Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, 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.

8.2 Labor and Delivery

There are no adequate and well-controlled studies with OFIRMEV during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

8.3 Nursing Mothers

While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 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. Caution should be exercised when OFIRMEV is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age *[see Dosage and Administration (2.3) and Pharmacokinetics (12.3)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12)]*. A reduced total daily dose of acetaminophen may be warranted.

8.7 Patients with Renal Impairment

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

10 OVERDOSAGE

Signs and Symptoms

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. 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.

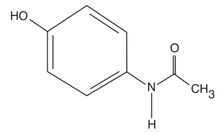
Treatment

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

For additional information, call a poison control center at 1-800-222-1222.

11 DESCRIPTION

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular weight of 151.16. Its structural formula is:



OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, and 10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.

Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

12.3 Pharmacokinetics

Distribution

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration (C_{max}) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the C_{max} following administration of OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

Pharmacokinetic parameters of OFIRMEV (AUC, C_{max}, terminal elimination half-life [$T_{½}$], systemic clearance [CL], and volume of distribution at steady state [Vss]) following administration of a single intravenous dose of 15 mg/kg for the pediatric population and 1000 mg in adults are summarized in Table 4.

Table 4. OFIRMEV Pharmacokinetic Parameters

Subpopulations	Mean (SD)				
	AUC (µg × h/mL)	C_{max} (µg/mL)	$T_{½}$ (h)	CL (L/h/kg)	Vss (L/kg)
Neonates	62 (11)	25 (4)	7.0 (2.7)	0.12 (0.04)	1.1 (0.2)
Infants	57 (54)	29 (24)	4.2 (2.9)	0.29 (0.15)	1.1 (0.3)
Children	38 (8)	29 (7)	3.0 (1.5)	0.34 (0.10)	1.2 (0.3)
Adolescents	41 (7)	31 (9)	2.9 (0.7)	0.29 (0.08)	1.1 (0.3)
Adults	43 (11)	28 (21)	2.4 (0.6)	0.27 (0.08)	0.8 (0.2)

The pharmacokinetic exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

Metabolism and Excretion

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: Conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450 enzyme pathway, primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). With therapeutic doses, NAPQI undergoes rapid conjugation with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates.

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen and more than 90% of the administered dose is excreted within 24 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. 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

In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss 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

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

Pain Study 2 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg every 6 hours or 650 mg every 4 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Patients receiving OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

14.2 Adult Fever

The efficacy of OFIRMEV 1000 mg in the treatment of adult fever was evaluated in one randomized, double-blind, placebo-controlled clinical trial. The study was a 6-hour, single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated through 6 hours in comparison to placebo. The mean temperature over time is shown in Figure 1.

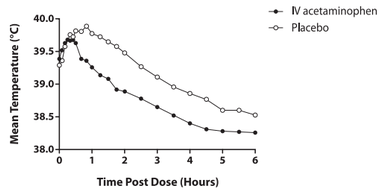


Figure 1: Mean Temperature (°C) Over Time

14.3 Pediatric Acute Pain and Fever

OFIRMEV was studied in 355 pediatric patients in two active-controlled and three open-label safety and pharmacokinetic trials *[see Use in Specific Populations (8.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 43825-102-01 - OFIRMEV® (acetaminophen) Injection is supplied in a 100 mL glass vial containing 1000 mg acetaminophen (10 mg/mL) in cartons of 24 vials.

OFIRMEV should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

For single use only. The product should be used within 6 hours after opening. Do not refrigerate or freeze.

Manufactured for:
Mallinckrodt Hospital Products Inc.
Hazelwood, MO 63042 USA

Revised: 12/2014

U.S. PATENT NUMBERS:
6,028,222; 6,992,218
OFV1569MK

Mallinckrodt™ Pharmaceuticals

XARTEMIS™ XR CII
(oxycodone hydrochloride and acetaminophen)
Extended-Release Tablets
012982

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012982

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; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and HEPATOTOXICITY

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 each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **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. (5.2)**
- **Accidental consumption of XARTEMIS XR, especially in children, can result in fatal overdose of oxycodone. (5.2)**
- **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 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. (5.3)**
- **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 the maximum daily limit, and often involve more than one acetaminophen-containing product. (5.7, 5.11)**

---------------------------- 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, misuse, overdose, and death 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. (1)

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

- The recommended dose of XARTEMIS XR is 2 tablets every 12 hours without regard to food. (2)
- XARTEMIS XR tablets should be swallowed whole. Do not break, chew, crush, cut, dissolve or split, the tablets. Swallow with enough water to ensure complete swallowing immediately after placing in mouth. (2)

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

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

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

- Patients who have known hypersensitivity to oxycodone, acetaminophen or any other components of the product. (4)
- Patients who have significant respiratory depression. (4)
- Patients who have acute or severe bronchial asthma or hypercarbia. (4)
- Patients who have suspected or known paralytic ileus. (4)

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

- XARTEMIS XR is not interchangeable with other oxycodone/acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration. (5)
- Controlled substance: XARTEMIS XR is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.1)
- Accidental exposure, especially in children, can result in fatal overdose of oxycodone. (5.2)
- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Use with caution in patients who are receiving other CNS depressants. (5.4, 7.1)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Use caution when administering in patients with hepatic impairment. (5.7)
- May cause serious skin reactions. Discontinue use if reaction occurs. (5.8)
- May worsen increased intracranial pressure and obscure its signs, such as level of consciousness or pupillary signs. (5.9)
- May cause hypotension. Use with caution in patients at increased risk of hypotension and in patients in circulatory shock. (5.10)
- Due to the potential for acetaminophen hepatotoxicity at doses higher than 4000 mg/day, XARTEMIS XR should not be used with other acetaminophen-containing products. (5.11)
- Discontinue XARTEMIS XR immediately if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.12)
- Use with caution in patients with biliary tract disease, including acute pancreatitis. (5.14)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.15)
- May impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. (5.16)

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

The most common adverse events with XARTEMIS XR are nausea, dizziness, headache, vomiting, constipation and somnolence. (6.1)

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 -------------------------------

- Concurrent use of other CNS depressants may cause respiratory depression, hypotension, and profound sedation or coma. (7.1)
- XARTEMIS XR may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. (7.2)
- Monoamine oxidase inhibitors may intensify the effects of opioids causing anxiety, confusion and significant depression of respiration or coma. (7.3)
- The CYP3A4 isoenzyme plays a major role in the metabolism of XARTEMIS XR; drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. (7.4)
- Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients. (7.5)
- Anticholinergics may increase risk for urinary retention and severe constipation. (7.6)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Labor and Delivery: Not recommended for use in women immediately prior to and during labor and delivery. (8.2)
- Nursing Mothers: Discontinue nursing or discontinue drug. (8.3)
- Geriatric use: Dose with caution as clearance of oxycodone may be slightly reduced in this population. (8.5)
- Hepatic impairment: Dose initiation should follow a conservative approach. (8.6)
- Renal impairment: Dose initiation should follow a conservative approach. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: March 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and HEPATOTOXICITY

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 or conditions *[see Warnings and Precautions (5.1)]*.

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 (5.2)]*.

Accidental Exposure

Accidental ingestion of XARTEMIS XR, especially in children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*.

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 the maximum daily limit, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.7, 5.11)]*.

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, misuse, overdose, and death 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.

2 DOSAGE AND ADMINISTRATION

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

2.1 Initial Dosage

Initiate the dosing regimen for each patient individually, taking into account the patient's 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 24-72 hours of initiating therapy with XARTEMIS XR *[see Warnings and Precautions (5.2)]*.

Use of XARTEMIS XR as the First Opioid Analgesic

The recommended dose 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.

XARTEMIS XR is given orally. XARTEMIS XR tablets should be swallowed 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 4000 milligrams.

2.2 Hepatic Impairment

In patients with hepatic impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression *[see Clinical Pharmacology (12.3)]*.

2.3 Renal Impairment

In patients with renal impairment start with one tablet and adjust dosage as needed. Monitor closely for respiratory depression *[see Clinical Pharmacology (12.3)]*.

2.4 Cessation of Therapy

When a patient who has been taking XARTEMIS XR regularly and may be physically dependent no longer requires therapy with XARTEMIS XR use a gradual downward titration of the dose of 50% every 2 to 4 days to prevent signs and symptoms of withdrawal. Do not stop XARTEMIS XR abruptly in patients who may be physically dependent.

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
- Known hypersensitivity to oxycodone, acetaminophen, or any other component of this product *[see Warnings and Precautions (5.12)]*.
- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia
- Known or suspected paralytic ileus

5 WARNINGS AND PRECAUTIONS

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

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 and in those who obtain the drug illicitly. 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 or 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 prescribing of XARTEMIS XR for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations 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.

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 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 dose increase. Closely monitor patients for respiratory depression when 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 consumption of XARTEMIS XR, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of XARTEMIS XR during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, 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.

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.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if XARTEMIS XR is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of XARTEMIS XR in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin XARTEMIS XR is made, start with XARTEMIS XR 1 tablet every 12 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1)]*.

5.5 Elderly, Cachectic, and 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. 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 (5.2)]*.

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with XARTEMIS XR, as in these patients, even usual therapeutic doses of XARTEMIS XR may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 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 4000 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 1300 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 4000 milligrams of acetaminophen per day, even if they feel well.

5.8 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 use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

5.10 Hypotensive Effect

Oxycodone may cause severe hypotension particularly in individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs which compromise vasomotor tone such as phenothiazines. Administer XARTEMIS XR with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure. XARTEMIS XR may produce orthostatic hypotension in ambulatory patients *[see Drug Interactions (7.1)]*.

5.11 Use With Other Acetaminophen-containing Products

The typical daily acetaminophen-contribution from XARTEMIS XR is 1300 mg. Due to the potential for acetaminophen hepatotoxicity at doses higher than 4000 milligrams/day, XARTEMIS XR should not be used concomitantly with other acetaminophen-containing products.

5.12 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.

5.13 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.

5.14 Gastrointestinal Effects

XARTEMIS XR is contraindicated in patients with known or suspected paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of XARTEMIS XR may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may cause spasm of the Sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

5.15 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of XARTEMIS XR, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

Inhibition of CYP3A4 activity by its inhibitors, 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 effects. These effects could be more pronounced with concomitant use of CYP 2D6 and 3A4 inhibitors.

Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, resulting in a potential lack of efficacy.

If co-administration is necessary, caution is advised when initiating XARTEMIS XR treatment in patients currently taking, or discontinuing CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.4)]*.

5.16 Driving and Operating Machinery

XARTEMIS XR may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

6 ADVERSE REACTIONS

The following treatment-emergent adverse reactions are discussed in more detail in other sections of the labeling:
- Respiratory Depression *[see Contraindications (4), Warnings and Precautions (5.2), and Overdosage (10)]*
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Use With Other Acetaminophen-containing Products *[see Warnings and Precautions (5.11)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies 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.

6.2 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

7 DRUG INTERACTIONS

7.1 CNS Depressants

The concomitant use of XARTEMIS XR with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and XARTEMIS XR for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

7.2 Neuromuscular Blocking Agents

Oxycodone, as well as other opioid analgesics, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

7.3 Monoamine Oxidase Inhibitors

Monoamine Oxidase Inhibitors (MAOIs) have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion, and significant depression of respiration or coma. The use of XARTEMIS XR is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

7.4 Agents Affecting Cytochrome P450 Enzymes

CYP3A4 Inhibitors

Because the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with XARTEMIS XR is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

CYP3A4 Inducers

CYP450 3A4 inducers may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. If co-administration with XARTEMIS XR is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the Cytochrome P450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs, including amiodarone and quinidine, and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction *[see Clinical Pharmacology (12.3)]*.

7.5 Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with an opioid agonist analgesic such as XARTEMIS XR. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of XARTEMIS XR and/or may precipitate withdrawal symptoms in these patients.

7.6 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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. All pregnancies, regardless of drug exposure, have a background risk of 2 to 4% for major birth defects, and 15 to 20% for pregnancy loss.

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. Reproductive studies in rats and rabbits with doses of oxycodone greater than clinical doses did not show any teratogenic or embryo-fetal toxic effects. XARTEMIS XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. XARTEMIS XR is not recommended for use in women during or immediately prior to labor. Neonates, whose mothers received opioid analgesics during labor, must be observed closely for signs of respiratory depression. An opioid antagonist such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate.

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. Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults based on a body surface area comparison) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg based on body surface area comparison), it was non teratogenic or embryo-fetal toxic.

8.3 Nursing Mothers

Oxycodone is present in human milk and may result in accumulation and toxicities such as sedation and respiratory depression in some infants. 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. Because of the potential for serious adverse reactions in nursing infants from XARTEMIS XR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of XARTEMIS XR in pediatric patients under the age of 18 years have not been established.

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.

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 start with one tablet and adjust the dosage as needed. Monitor closely for respiratory depression *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Information from oxycodone HCl indicates that patients with renal impairment (defined as a creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function.

In patients with renal impairment start with one tablet and adjust the dosage as needed. Monitor closely for respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XARTEMIS XR contains oxycodone, a mu-opioid agonist of the morphine type and is a Schedule II controlled substance. XARTEMIS XR is subject to misuse, abuse, addiction and criminal diversion *[see Warnings and Precautions (5.1)]*.

9.2 Abuse

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.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build-up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: 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 abuse 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" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

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 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 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 intended 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

Patients may exhibit tolerance to some of the effects of oxycodone. 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 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 or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other 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. In patients suspected of having significant physical dependence, withdrawal symptoms may be reduced by tapering therapy.

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

10.1 Signs and Symptoms

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

Oxycodone

Acute overdosage with opioids 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, 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.

10.2 Treatment

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

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdose or unusual sensitivity to opioids, including oxycodone. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on XARTEMIS XR. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced 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 agonist should be begun with care and by titration with smaller than usual doses of the agonist.

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.

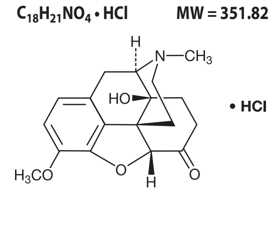
Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

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.

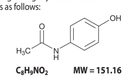
Oxycodone hydrochloride, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride, is an opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine. The structural formula for oxycodone hydrochloride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

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



• HCl

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

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 Central Nervous System

Oxycodone produces respiratory depression by direct action on brainstem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. 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 due to hypoxia in overdose situations.

Effects on 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 may cause a decrease in the secretion of hydrochloric acid in the stomach that reduces motility while increasing the tone of 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 Cardiovascular System

Oxycodone, in therapeutic doses, produces peripheral vasodilation (arterial and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats, and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown.

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 (8.3)]*.

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.

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 (5.4, 5.15)]*.

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.

Elimination

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

Elderly: 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.

Gender: 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 (defined as creatinine clearance <60 mL/min) 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 APAP, the components of XARTEMIS XR. The following data are based on findings from studies performed with the individual components.

Carcinogenesis

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

No animal studies to evaluate the effect of oxycodone on male or female fertility have been conducted.

In studies 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.

Bottles of 100 NDC 23635-115-01

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

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Provide the following information to patients receiving XARTEMIS XR or their caregivers:

Proper Administration

Inform patients that XARTEMIS XR is not interchangeable with other forms of oxycodone/acetaminophen.

Inform patients XARTEMIS XR is a narcotic pain reliever and must be taken only as directed.

Inform patients to 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.

Inform patients that XARTEMIS XR tablets must be swallowed 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.

Inform patients that 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.

Inform patients not to adjust the dose of XARTEMIS XR without consulting with a physician or other healthcare professional.

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

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 of 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 doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Consumption

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store XARTEMIS XR securely and to dispose of unused XARTEMIS XR by flushing the tablets down the toilet.

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 (5.3)]*.

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if XARTEMIS XR is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Impairment of Mental or Physical Ability

Inform patients that XARTEMIS XR may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery). Advise patients started on XARTEMIS XR or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.

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.

Information Regarding Nursing

Advise women to not breastfeed as breastfeeding may cause sedation in the infant.

Cessation of Therapy

If patients have been receiving treatment with XARTEMIS XR for more than a few weeks and cessation of therapy is indicated, counsel them on the possibility of withdrawal and provide medical support for safe discontinuation of the product.

Common Side Effects

Advise patients taking XARTEMIS XR of the potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.

Advise patients of the most common adverse reactions that may occur while taking XARTEMIS XR: nausea, dizziness, headache, vomiting, constipation and somnolence.

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

Mallinckrodt™ Pharmaceuticals

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.
- 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.
- 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 life-threatening withdrawal symptoms in your newborn baby if not recognized and treated.
- **breastfeeding.** XARTEMIS XR passes into breast milk and 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.

When taking XARTEMIS XR:

- Do not change your dose. Take XARTEMIS XR exactly as prescribed by your healthcare provider.
- 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.
- **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.
- Do not take other products that contain acetaminophen while taking XARTEMIS XR.

The possible side effects of XARTEMIS XR are:

- nausea, dizziness, headache, vomiting, constipation, sleepiness. 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, low blood pressure when changing positions, or you are feeling faint.
- 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**

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