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 dosing guidelines.

**Prescription intravenous product containing acetaminophen**

**OFIRMEV® (acetaminophen) injection**

**Prescription oral products containing acetaminophen (examples)**

**Acetaminophen and Oxycodone Combinations**
- Endocet®
- Percocet®
- Primlev®
- Roxicet®
- XARTEMS™ XR

**Acetaminophen and Hydrocodone Combinations**
- Lorct®
- Norco®
- Vicodin® ES
- Xodol®
- Loratab®
- Vicodin®
- Vicodin® HP
- Zamicet®

**Acetaminophen and Butalbital Combinations**
- Bupap®
- Tencon®

**Acetaminophen, Butalbital, and Caffeine Combinations**
- Dolict® Plus
- Esic®
- 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
- ElxiSure® 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
- O-Pap® (various products under this brand name)
- RapiMed®

**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, 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.

**Important Risk Information**

**Warning: Addiction, Abuse, and Misuse; Life-Threatening Respiratory Depression; Accidental Exposure; Neonatal Opioid Withdrawal Syndrome; and Hepatotoxicity**

**Addiction, Abuse, and Misuse**

XARTEMS™ 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 XARTEMS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate.

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMS XR. Monitor for respiratory depression, especially during initiation of XARTEMS XR or following a dose increase. Instruct patients to swallow XARTEMS XR tablets whole; crushing, chewing, or dissolving XARTEMS XR can cause rapid release and absorption of a potentially fatal dose of oxycodone.

**Accidental Exposure**

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

**Neonatal Opioid Withdrawal Syndrome**

Prolonged use of XARTEMS 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**

XARTEMS 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 XARTEMS™ XR and in accompanying Full Prescribing Information for each product.
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 aneptaxis.

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 hypercapnia.
  - 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 than 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 who have a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing 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 mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in mouth.
• Use in Patients with Obstructive Sleep Apnea: Opioids may cause sleep apnea, and sleep apnea may be exacerbated by the use of acetaminophen-containing analgesics. Consider the use of continuous positive airway pressure (CPAP) for the treatment of sleep apnea.

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 psychophysiologic 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.
OFFRMEV® (acetaminophen) injection is contraindicated for:

- Management of mild to moderate pain (1)
7 DRUG INTERACTIONS
7.1 Effects of other Substances on Acetaminophen

Sodium warfarin, an anticoagulant, has been shown to have drug interactions with acetaminophen resulting in an increased risk of hemorrhage and the potential for fatal outcomes. Acetaminophen is metabolized to its toxic metabolite and pharmacokinetic data were collected in 355 patients experiencing a statistically significant greater reduction in pain intensity over 24 hours compared to placebo. However, this was not demonstrated in a study evaluating the efficacy of OFIRMEV 1000 mg in the treatment of adult fever (see USP Controlled Room Temperature) for use in healthy adults. There is limited evidence that acetaminophen is mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested negative in the in vitro chromosomal aberration assay using human lymphocytes. In Clinical Pharmacology (12.2), a reduced total daily dose of acetaminophen may be warranted.

8.5 Geriatric Use

The maximum concentration (Cmax) occurs at the end of the 1-3 hour period following an oral dose of OFIRMEV. Compared to the same dose of oral acetaminophen, the Cmax following a single oral dose of 1000 mg of OFIRMEV was 19.7 (8.2) mg/mL at 30 minutes, 25.6 (8.0) mg/mL at 60 minutes, and 38.0 (8.2) mg/mL at 120 minutes. Doses of oral acetaminophen.

8.7 Patients with Renal Impairment

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 65 years. The pharmacokinetic profile of OFIRMEV is generally similar in adults and premature neonates following administration of single doses of 500, 650, and 800 mg.

The pharmacokinetics of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 243 healthy male and female adults with a mean age of 41 years is shown in Figure 1. The area under the concentration-time curve (AUC) was statistically significantly greater with the OFIRMEV 1000 mg dose compared to placebo (p < 0.0001). The mean (SD) minimum concentration (Cmin) was 139 (45) μg/mL after oral administration of 1000 mg OFIRMEV.

Table 4. OFIRMEV Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>AUC (μg · h/mL)</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Volume (L)</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>T1/2 (h)</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>10.8 (5.2)</td>
<td>3.2 to 28</td>
<td>19</td>
<td>1.2 (0.2)</td>
<td>0.7 to 1.9</td>
<td>1.6 to 2.5</td>
<td>1.7 (0.3)</td>
<td>1.0 to 2.7</td>
<td></td>
</tr>
<tr>
<td>650</td>
<td>17.3 (5.6)</td>
<td>6.0 to 35</td>
<td>24</td>
<td>1.7 (0.3)</td>
<td>1.2 to 2.3</td>
<td>2.0 to 3.0</td>
<td>2.2 (0.5)</td>
<td>1.5 to 3.2</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>35.6 (9.8)</td>
<td>11.0 to 70</td>
<td>36</td>
<td>2.1 (0.3)</td>
<td>1.5 to 2.8</td>
<td>2.4 to 3.4</td>
<td>2.7 (0.5)</td>
<td>1.8 to 3.6</td>
<td></td>
</tr>
</tbody>
</table>

The pharmacokinetic exposure of OFIRMEV observed in elderly patients is shown in Figure 2. The Cmax and AUC of OFIRMEV 1000 mg increased in elderly patients compared to young adults (Table 4). There was no evidence of a change in pharmacokinetics with increasing age in patients up to the age of 84 years; however, a change in pharmacokinetics with increasing age was observed in patients aged 65 years and older.

6.7, 8.5, and 8.6), placental transport of OFIRMEV, and the metabolism of OFIRMEV by placental cytochrome P450 3A4, which is variably expressed in human placentas, has been demonstrated in human placental tissue cultures. The study was a 4-hour, single-dose, endotoxin-induced fever study in 6 healthy adult males. A statistically significant antipyretic effect of 1000 mg of OFIRMEV was demonstrated in 18 healthy male volunteers, with a mean (SD) decrease in body temperature of 0.7 (0.2) °C at 120 minutes after oral administration of 1000 mg OFIRMEV.

The pharmacokinetic exposure of OFIRMEV observed in such patients is shown in Table 5. The Cmax and AUC of OFIRMEV 1000 mg increased in patients with impaired renal function (Table 4). There was no evidence of a change in pharmacokinetics with increasing age in patients up to the age of 84 years; however, a change in pharmacokinetics with increasing age was observed in patients aged 65 years and older.

The pharmacokinetic exposure of OFIRMEV observed in elderly patients is shown in Figure 2. The Cmax and AUC of OFIRMEV 1000 mg increased in elderly patients compared to young adults (Table 4). There was no evidence of a change in pharmacokinetics with increasing age in patients up to the age of 84 years; however, a change in pharmacokinetics with increasing age was observed in patients aged 65 years and older.

The pharmacokinetic exposure of OFIRMEV observed in elderly patients is shown in Figure 2. The Cmax and AUC of OFIRMEV 1000 mg increased in elderly patients compared to young adults (Table 4). There was no evidence of a change in pharmacokinetics with increasing age in patients up to the age of 84 years; however, a change in pharmacokinetics with increasing age was observed in patients aged 65 years and older.
5.11 Use With Other Acetaminophen-containing Products

Extended-release tablets (oxycodone hydrochloride/acetaminophen): the respiratory depressant effects of narcotics and their capacity to elevate serum levels of pressure increased, gamma-glutamyltransferase increased, liver functional studies in pregnant rats that received oral acetaminophen during organo-