HIGHLIGHTS OF PRESCRIBING INFORMATION

OFIRMEV®
(acetaminophen) injection

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

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)

 Dosage and Administration

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

• 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)

• Take care when prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death. (5.3)

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)

 Usage in Specific Populations

• Pediatric Use: The effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established. The safety and effectiveness of OFIRMEV in pediatric patients 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)

Full Prescribing Information: Contents*

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Revised: 03/2018
Table 2. Dosing for Children

<table>
<thead>
<tr>
<th>Age group</th>
<th>Dose given every 6 hours</th>
<th>Maximum total daily dose of acetaminophen (by all routes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (29 days to 2 years)</td>
<td>12.5 mg/kg</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Infants (29 days to 2 years)</td>
<td>15 mg/kg</td>
<td>80 mg/kg</td>
</tr>
</tbody>
</table>

2.5 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 or a non-vented intravenous set through the administration spike port of the 100 mL bag. OFIRMEV may be administered without further dilution. Examine the container contents before dose preparation or administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the container 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 container 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 container 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 container of OFIRMEV is not intended for use in patients weighing less than 50 kg. OFIRMEV is supplied in a single-dose container 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 container seal has been penetrated, or the contents transferred to another container, administer the dose of OFIRMEV within 6 hours.

For bags, refrain from applying excessive pressure causing distortion to the bag, such as wringing or twisting, since such handling could result in breakage of the bag.

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 or 100 mL bag 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 known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.

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 dosage 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 are 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published epidemiological studies with oral acetaminophen use during pregnancy have not reported a clear association with acetaminophen use and birth defects. Few studies have evaluated maternal or adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

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, indicated no increased risk of 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 4,300 children in the control group. Other epidemiological data showed similar results. However, these studies cannot definitively establish the absence of any risk because of methodological limitations, including recall bias.

Animal Data

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 and increases in bone-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 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 due to postnatal and post-weighing 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 Lactation

Risk Summary

There is no information regarding the presence of OFIRMEV in human milk, the effects on the breastfed infant, or the effects on milk production. However, limited published studies report that acetaminophen passes rapidly into human milk with similar levels in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral administration of 1 gram APAP. 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. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OFIRMEV and any potential adverse effects on the breastfed infant from OFIRMEV or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on animal data use of acetaminophen may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible. Published animal studies reported that oral acetaminophen treatment of male rats 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, and reduced fertility. In female animals given the same doses, reduced implantation sites were reported. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposure [see Nonclinical Toxicology (13.1)].
8.4 Pediatric Use

**Treatment of Acute Pain**

The safety and effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults and safety and pharmacokinetic data from adult and 483 pediatric patients across all age groups [see Dosage and Administration (2.3) and Pharmacokinetics (12.3)].

The effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.

In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.

**Treatment of Fever**

The safety and effectiveness of OFIRMEV for the treatment of fever in pediatric patients, including premature neonates born at ≥ 32 weeks gestational age is supported by adequate and well-controlled studies of OFIRMEV in adults, clinical studies in 244 pediatric patients 2 years and older, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age.

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 OVERDOSE

**Signs and Symptoms**

In acute acetaminophen overdose, 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 antipyrhetic 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:

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OH
O
N
CH3
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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.
In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.06 times the MHDD, based on a body surface area comparison) reduced the number of primordial follicles in female offspring and reduced the percentage of full term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

In a published study, oral administration of 350 mg/kg acetaminophen to pregnant rats (0.85 times the MHDD, based on a body surface area comparison) from Gestation Day 13 to 21 (dams) reduced the number of germ cells in the fetal ovary, decreased ovary weight, and reduced the number of pups per litter in F1 females as well as reduced ovary weights in F2 females.

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](image)

14.3 Pediatric Acute Pain and Fever

OFIRMEV was studied in pediatric patients in three active-controlled trials 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.

NDC 43825-102-03 - OFIRMEV (acetaminophen) Injection is supplied in a 100 mL bag containing 1000 mg acetaminophen (10 mg/mL) in cartons of 24 bags.

Do not remove unit from overwrap until ready for use.

To open, tear outer wrap at the notch and remove solution bag. After removing the outer wrap, check the container for minute leaks by squeezing the solution bag firmly. If leaks are found, discard the solution because the sterility may be impaired. A small amount of moisture may be present inside the outer wrap.

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

For single-dose 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

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