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

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 old: 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 may result in hepatic injury, including the risk of severe hepatotoxicity and death. (5.1)
- Do not exceed the maximum recommended daily dose of acetaminophen. (5.1)
- 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 if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2)

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 Cadence Pharmaceuticals Inc. at 1-877-647-2239 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: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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. The maximum daily dose of acetaminophen is based on all routes of administration (i.e. intravenous, oral, and rectal) and all products containing acetaminophen.

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.

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.

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 any 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.

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 severe hepatotoxicity and death [*see OVERDOSAGE (10)*]. Do not exceed the maximum recommended daily dose of acetaminophen [*see DOSAGE AND ADMINISTRATION (2)*].

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 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)*]
- Allergy and Hypersensitivity [*see WARNINGS AND PRECAUTIONS (5.2)*]

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 2. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Table 2. Treatment-Emergent Adverse Reactions Occurring ≥ 3% in OFIRMEV 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).

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 - Recommended Dosage: Children (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), 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.

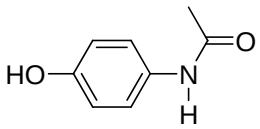
Treatment

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, 10.4 mg dibasic sodium phosphate, anhydrous, 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 3.

Table 3. 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 l000 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.

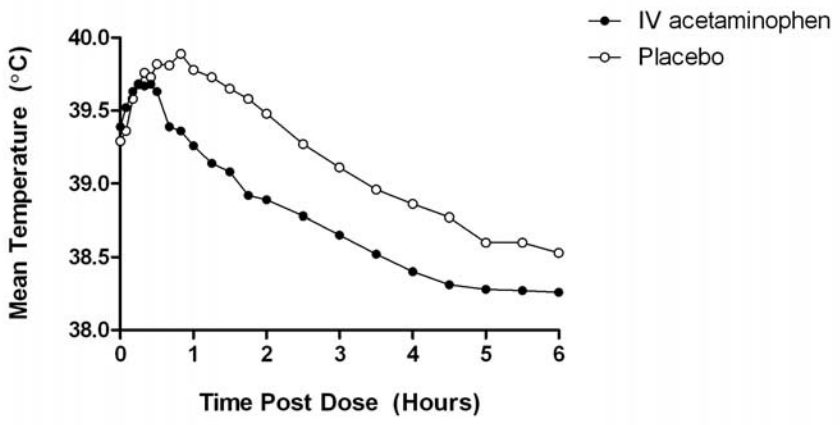


Figure 1: Mean Temperature (°C) Over Time

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 PEDIATRIC USE (8.4)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Label part number

OFIRMEV (acetaminophen) injection

Manufactured for:
Cadence Pharmaceuticals, Inc.
San Diego, CA 92130

Revised: 11/2010