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.

Please see additional Important Risk Information, including complete boxed warning, on reverse and in accompanying Full Prescribing Information.
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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.

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.

To report Suspected adverse Reactions, contact Mallinckrodt Pharmaceuticals at 1.800.778.7898 or FDA at 1.800.FDA.1088 or www.fda.gov/medwatch.

Please see accompanying Full Prescribing Information, including complete boxed warning.
7.1 Effects of other Substances on Acetaminophen

6.1 Clinical Trial Experience

5.3 Risk of Medication Errors

3 DOSAGE FORMS AND STRENGTHS

2.2 Recommended Dosage: Children

- Adults and Adolescents Weighing 50 kg and Over:
  - 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum recommended (by all routes of administration and from all acetaminophen-containing products including combination products).

- In patients with severe hepatic impairment or severe active liver disease
  - The maximum total daily dose of acetaminophen from all products should not exceed maximum daily limits, and often involve more than one acetaminophen-containing product (5.1).

- For adult and adolescent patients weighing ≥ 50 kg
  - 15 mg/kg, a minimum dosing interval of 4 hours, and the unused portion must be discarded.

- The entire 100 mL vial of OFIRMEV is not intended for use in a single patient.

- To report SUSPECTED ADVERSE REACTIONS, contact Multicellular Health Products Inc. at 1-800-768-7065 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- A total of 355 pediatric patients (47 neonates, 64 infants, and 244 children) have received OFIRMEV.

- The following serious adverse reactions are discussed elsewhere in the labeling:
  - Other Adverse Reactions Observed During Clinical Studies of OFIRMEV: Hives, disseminated intravascular coagulation, anaphylaxis, hypotension, and angioedema.

- Observations of potentially related adverse events were reported by adult subjects treated with OFIRMEV.

- The frequency of serious adverse reactions was noted.

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

- OFIRMEV is a sterile, colorless, non-pyrogenic, non-degassed, non-aqueous solution.

- OFIRMEV is intended for intravenous use only.

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- In randomized clinical trials, including 37.3% (n=380) who received 5 or more doses of OFIRMEV, the maximum number of doses received was 15.

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There are no adequate and well-controlled studies with the next generation pups of litters per mating pair, male offspring with an increased 1430 mg/kg/day). These doses are approximately 0.43, 0.87, 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and skeletal malformations. When pregnant women; however, epidemiological data on oral acetaminophen use and recurred when she resumed acetaminophen use. It is not known whether OFIRMEV can cause fetal harm when 3000 mg and repeated doses of oral acetaminophen. A reduced total daily dose of acetaminophen level is below the lower line.

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. Acetaminophen has been shown to have analgesic and antipruritic actions 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 in man have no delayed effect on small-vessel hemostasis. Clinical studies of both active liver disease and severe active liver disease and should not be used in patients with hepatic impairment or severe active liver disease (see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)). A reduced total daily dose of acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of monocellular cell leukemia at 8 times the maximum human daily dose (MHDD) of 4g/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (3.7 times the MHDD, based on a body surface area comparison).

The pharmacokinetics of OFIRMEV have been studied in infants and children age 2 years and older. The pharmacokinetic exposure of OFIRMEV observed in 101 patients with moderate to severe pain following total of 27.0% to 77.3% (see USP Controlled Room Temperature). For single-dose on singledose, endotoxin-induced fever study in 60 healthy volunteers, the mean temperature over time is shown in Figure 1. A reduced total daily dose of acetaminophen up to 70% higher, while overall pharmacokinetic data were collected in 355 patients and 60 healthy volunteers was compared to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, there was no evidence of carcinogenic activity based on increased incidences of bronchial and tracheal carcinoma in mice. 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 monocellular cell leukemia at 8 times the maximum human daily dose (MHDD) of 4g/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (3.7 times the MHDD, based on a body surface area comparison).

OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours. There was an attenuation in decrease in opioid consumption, the clinical benefit of which was not demonstrated.

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for nonchromosomal aberration assay using human lymphocytes. In Clinical Pharmacology (1.2). A reduced total daily dose of acetaminophen may be warranted.

had no increased risk of major birth defects among pregnant women admitted 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 24,424 women with live born singletons who were exposed to oral acetaminophen during pregnancy, demonstrated a threshold effect. Clinical studies of both active liver disease and severe active liver disease (see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)). A reduced total daily dose of acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of monocellular cell leukemia at 8 times the maximum human daily dose (MHDD) of 4g/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (3.7 times the MHDD, based on a body surface area comparison).