OFIRMEV® from the start

Consider administering OFIRMEV pre-op, then scheduling q6h.

TRANSITION TO ORAL ANALGESIA WHEN:

• Compromised GI absorption or inability to take
• Parenteral analgesia is clinically warranted

Utilization considerations: Consider beginning your multimodal analgesic regimen with OFIRMEV.

CONTINUE WITH OFIRMEV®

Pain follows the acute and chronic analgesic.

Schedule OFIRMEV® q6h for the first 24 h as long as clinically warranted.

Continuation considerations:

• Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors

• OFIRMEV dosing information

• OFIRMEV pharmacokinetic and clinical information

• OFIRMEV®—a non-opioid, non-NSAID, intravenous analgesic for the management of pain

An overview of:

• Expert weights and measures in pain management
• Mechanism of action and clinical function of ofirmev
• OFIRMEV pharmacists and clinical information
• OFIRMEV®—a non-opioid, non-NSAID, intravenous analgesic for the management of pain

INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for the management of mild to moderate pain, management of moderate to severe pain, and reduction of fever. OFIRMEV® [package insert]. San Diego, CA: Mallinckrodt company; 2013.

IMPORTANT RISK INFORMATION

• Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease.
• 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.
• Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.

WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

Utilization considerations:

• Be aware of patient’s renal and hepatic function.
• Be aware of patient’s risk factors for hepatic injury.
• Be aware of maximum acetaminophen daily dose.
• Be aware of potential drug interactions.
• Be aware of potential for hepatic injury.
• Be aware of the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

Use OFIRMEV® for the treatment of acute pain and fever that has not been studied in patients 2 years of age or younger.

FOR PHARMACY PROFESSIONALS

Please see additional Important Risk Information, including complete boxed warning, in accompanying Full Prescribing Information.
Despite pain management, many patients still experience postoperative pain

In a 2012 survey, approximately 85% of patients reported post-op pain, with a total of 65% reporting pain as moderate to extreme.

Pain management goals are multifaceted.

Follow American Society of Anesthesiologists guidelines:

- Facilitate safe and effective acute pain management in the perioperative setting
- Maintain patient's functional abilities

Employ a multimodal approach for acute pain management:

- Use non-opioid analgesics alone in mild to moderate pain, or with adjunctive opioids in moderate to severe pain
- Begin pain management prior to surgery
- Multimodal analgesia may decrease opioid dose requirements

**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 accompanying Full Prescribing Information, including complete boxed warning.

Multimodal analgesia in practice

American Society of Anesthesiologists (ASA) guidelines:

- The ASA Task Force recommends the use of multimodal analgesia whenever possible in the perioperative setting
- Patients should receive an around-the-clock regimen of acetaminophen, NSAIDs, or a COX-2 inhibitor within 30 minutes of surgery
- Opioids should be added in escalating doses if the level of analgesic is not adequate

Multimodal analgesia can help manage different levels of pain across the perioperative setting.

**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**

- 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.

Please see accompanying Full Prescribing Information, including complete boxed warning.
Despite pain management, many patients still experience postoperative pain. In a 2012 survey, approximately 85% of patients reported post-op pain, with a total of 65% reporting pain as moderate to extreme.

Pain management goals are multifaceted and follow American Society of Anesthesiologists guidelines:

- Facilitate safe and effective acute pain management in the perioperative setting
- Maintain patient's functional abilities
- Employ a multimodal approach for acute pain management
- Use non-opioid analgesics alone in mild to moderate pain, or with adjunctive opioids in moderate to severe pain

- Begin pain management prior to surgery
- Multimodal analgesia may decrease opioid dose requirements

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
- 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.

Please see accompanying Full Prescribing Information, including complete boxed warning.

Multimodal analgesia can help manage different levels of pain across the perioperative setting:

- Non-opioids, such as acetaminophen, NSAIDs, or COX-2 selective inhibitors, are the foundational analgesic agents given perioperatively for the management of pain; opioids are added for moderate to severe pain.

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
- 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.

Please see accompanying Full Prescribing Information, including complete boxed warning.
Consider beginning your IV analgesic regimen with OFIRMEV.

**INDICATIONS AND USAGE**

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

**CONTRAINdications**

- known hypersensitivity to acetaminophen or to any of the excipients in the intravenous (IV) formulation.
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

**ADVERSE REACTIONS**

- Common adverse reactions include nausea, vomiting, headache, and insomnia.
- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active renal impairment (creatinine clearance ≤ 30 mL/min).

**WARNINGS AND PRECAUTIONS**

- In particular, be careful to ensure that:
  - the dose in milligrams (mg) and milliliters (mL) is not confused;
  - the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

**IMPORTANT RISK INFORMATION**

- OFIRMEV®—a non-opioid, non-NSAID, intravenous analgesic for the management of pain

**FOR PHARMACY PROFESSIONALS**

- An overview of
  - severe pain in perioperative pain management
  - the role of OFIRMEV in perioperative pain management
  - OFIRMEV pharmaceuticals and clinical formulation
  - OFIRMEV for the management of pain
  - OFIRMEV during infusion

**INDICATIONS AND USAGE**

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

- Common adverse reactions include nausea, vomiting, headache, and insomnia.
- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.

**WARNINGS AND PRECAUTIONS**

- In particular, be careful to ensure that:
  - the dose in milligrams (mg) and milliliters (mL) is not confused;
  - the total daily dose of acetaminophen from all sources does not exceed maximum daily limits. Do not exceed the maximum recommended daily dose of acetaminophen. The maximum recommended daily dose of OFIRMEV for adults ≥50 kg is 4000 mg.

**ADVERSE REACTIONS**

- Common adverse reactions include nausea, vomiting, headache, and insomnia.
- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.

**CONTRAINdications**

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**ADVERSE REACTIONS**

- Common adverse reactions include nausea, vomiting, headache, and insomnia.
- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.
In pharmacokinetic studies

Greater peak levels with IV acetaminophen

**OFIRMEV® 1 g was associated with greater peak plasma levels**

Singla et al. Three-way, crossover, single-center, single-dose pharmacokinetic study of 6 healthy adult males. Each received 3 single-dose treatments of IV, oral, and rectal acetaminophen, separated by a washout period of 24 h. Treatment dosage was 1 g IV and oral acetaminophen, and 1300 mg rectal. IV acetaminophen was administered over 15 minutes commencing at 0 h. CSF and blood draws were performed prior to study medication administration and at 8 additional time points for 6 h in each treatment period.

*Rectal acetaminophen data reflect standardization of the 1300-mg dose to 1 g (linear kinetics).

- Peak plasma concentrations were 76% higher than oral acetaminophen \((P=0.0004)\) and 256% higher than rectal acetaminophen \((P<0.0001)\).  
- Efficacy was not assessed in this study

**OFIRMEV 1 g was associated with greater cerebrospinal fluid (CSF) levels**

Singla et al. Three-way, crossover, single-center, single-dose pharmacokinetic study of 6 healthy adult males. Each received 3 single-dose treatments of IV, oral, and rectal acetaminophen, separated by a washout period of 24 h. Treatment dosage was 1 g IV and oral acetaminophen, and 1300 mg rectal. IV acetaminophen was administered over 15 minutes commencing at 0 h. CSF and blood draws were performed prior to study medication administration and at 8 additional time points for 6 h in each treatment period.

*Rectal acetaminophen data reflect standardization of the 1300-mg dose to 1 g (linear kinetics).

- Peak CSF concentrations were 60% higher than oral acetaminophen \((P<0.0001)\) and 87% higher than rectal acetaminophen \((P<0.0001)\). No significant difference was seen between oral and rectal groups.  
- Efficacy was not assessed in this study

**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 accompanying Full Prescribing Information, including complete boxed warning.
**In an orthopaedic surgery study**

**Significant pain relief and reduced opioid consumption**

OFIRMEV® 1 g + PCA* morphine demonstrated significant pain relief vs placebo + PCA morphine

![Mean pain relief scores, single dose](image)

<table>
<thead>
<tr>
<th>Pain relief</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>1.8</td>
<td>3</td>
</tr>
</tbody>
</table>

Significant improvement over placebo + PCA morphine

P<0.05 at every time point

*Patient-controlled analgesia.

†SPID24=sum of pain intensity differences, based on VAS score, at 0 to 24 h.

**Significantly reduced pain intensity over 24 h**

- OFIRMEV showed a greater reduction in pain intensity over 24 h (SPID24)† compared to placebo (P<0.001)†

**OFIRMEV 1 g + PCA morphine significantly reduced morphine consumption vs placebo + PCA morphine**

![Reduction in morphine consumption](image)

<table>
<thead>
<tr>
<th>Morphine (mg)</th>
<th>Over 6 h</th>
<th>Over 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFIRMEV 1 g + PCA morphine (n=48)</td>
<td>17.8 mg</td>
<td>57.4 mg</td>
</tr>
<tr>
<td>Placebo + PCA morphine (n=52)</td>
<td>9.7 mg</td>
<td>38.3 mg</td>
</tr>
</tbody>
</table>

-33% and -46%

Sinatra et al. (Pain Study 1)
Randomized, double-blind, placebo-controlled, single- and repeated-dose 24-h study (n=101). Patients received OFIRMEV 1 g + PCA morphine or placebo + PCA morphine the morning following total hip or knee replacement surgery. Primary endpoint: pain relief measured on a 5-point verbal scale over 6 h. Morphine rescue was administered as needed.

P<0.05 at every time point.

The clinical benefit of reduced opioid consumption was not evaluated or demonstrated

**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 accompanying Full Prescribing Information, including complete boxed warning.
In an abdominal laparoscopy study

Reductions in pain intensity

OFIRMEV® 1 g + rescue significantly reduced pain intensity vs placebo + rescue over 24 h

Wininger et al. (Pain Study 2)
Randomized, double-blind, placebo-controlled, multicenter, parallel-group study. The morning following abdominal laparoscopic surgery, patients received OFIRMEV 1 g or placebo q6h or OFIRMEV 650 mg or placebo q4h. IV or oral rescue medication was available to all patients. Primary endpoint: SPID24 (sum of pain intensity differences, based on VAS score, from baseline, at 0 to 24 h).

OFIRMEV 1 g pain intensity scores at each dosing interval over 24 h

Wininger et al. (Pain Study 2)
Randomized, double-blind, placebo-controlled, multicenter, parallel-group study. The morning following abdominal laparoscopic surgery, patients received OFIRMEV 1 g or placebo q6h or OFIRMEV 650 mg or placebo q4h. IV or oral rescue medication was available to all patients. Primary endpoint: SPID24 (sum of pain intensity differences, based on VAS score, from baseline, at 0 to 24 h).

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

- 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.

Please see accompanying Full Prescribing Information, including complete boxed warning.
Recommended dosing of OFIRMEV®

### Dosing of OFIRMEV for adults, adolescents, and children ≥2 years old

<table>
<thead>
<tr>
<th>Age group</th>
<th>Dose given every 4 hours</th>
<th>Dose given every 6 hours</th>
<th>Maximum single dose</th>
<th>Maximum total daily dose of acetaminophen (by all routes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (13 years and older)</td>
<td>650 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
<td>4000 mg in 24 hours</td>
</tr>
<tr>
<td>weighing ≥50 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults and adolescents (13 years old and older)</td>
<td>12.5 mg/kg</td>
<td>15 mg/kg</td>
<td>15 mg/kg (up to 750 mg)</td>
<td>75 mg/kg in 24 hours (up to 3750 mg)</td>
</tr>
<tr>
<td>weighing &lt;50 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children 2 to 12 years of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Minimum dosing interval is q4h\(^6\)
- For instructions regarding q4h dosing, please see Full Prescribing Information\(^6\)
- No dose adjustment is required when transitioning to oral acetaminophen in adults and adolescents\(^6\)
- OFIRMEV should be administered only as a 15-minute infusion. Administer only as directed\(^6\)
- OFIRMEV should be stored at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]\(^6\)
- For single use only. The product should be used within 6 hours after opening\(^6\)
- OFIRMEV vial fits in the Pyxis\(^8\) Anesthesia System\(^*\) and other commonly used anesthesia/OR carts\(^1\)
  - Vial dimensions: 1.9” x 4.3”

### 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

**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.

Please see accompanying Full Prescribing Information, including complete boxed warning.
Consider beginning your IV analgesic regimen with OFIRMEV®

OFIRMEV® is indicated for the management of mild to moderate pain, management of postoperative pain, and fever. OFIRMEV pharmacokinetic and clinical information is discussed in the following sections.

Please see accompanying Full Prescribing Information, including complete boxed warning.
Consider administering OFIRMEV pre-op, then scheduling q6h.

Please see accompanying Full Prescribing Information, including complete boxed warning.

OFIRMEV® from the start

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.

Use in Specific Populations

• Common adverse reactions in adults include nausea, vomiting, headache, and insomnia.
• Common adverse reactions in children include fever, headache, and vomiting.
• The antipyretic effects of OFIRMEV may mask fever.
• Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), and hemorrhagic bullous eruption (HBE).
• Approximately 3% of patients with acetaminophen hypersensitivity have had anaphylactic reactions. Clinical signs included hypotension, bradycardia, and laryngeal edema.
• The anaphylactic reactions occurred within 1 hour of acetaminophen administration.
• Rarely, allergic reactions associated with the use of acetaminophen have been reported.

ADVERSE REACTIONS

• The dose of OFIRMEV for the treatment of each pain and fever has not been studied in pediatric patients. Please see accompanying Full Prescribing Information.

Please see accompanying Full Prescribing Information, including complete boxed warning.
WARNINGS AND PRECAUTIONS

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

INDICATIONS AND USAGE

• Acetaminophen is contraindicated:
  --------------------- CONTRAINDICATIONS ---------------------
  • Children:

HIGHLIGHTS OF PRESCRIBING INFORMATION

the recommended maximum daily limits, and often involve
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 fatal outcomes, in patients who used the drug with outra interventions that increase the risk of liver injury or in the presence of certain concomitant medical conditions (see Warnings and Precautions (5.1)).

the total daily dose of acetaminophen from all routes of administration and all acetaminophen-containing products including combination products may result in hepatic injury, including the risk of liver failure (see Warnings and Precautions (5.1), Deaths (7.1), and Precautions (17)).

• the dose in milligrams (mg) and milliliters (mL) is not confused;

• use caution when administering acetaminophen in patients with hepatic impairment or active liver disease.

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• if the dose in milligrams (mg) and milliliters (mL) is not confused;

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• the dose in milligrams (mg) and milliliters (mL) is not confused;

• if the dose in milligrams (mg) and milliliters (mL) is not confused;

• use caution when preparing, prescribing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death.
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 in lactating women, it is known that orally administered OFIRMEV is absorbed to an extent similar to that observed in the non-pregnant state. The plasma levels of acetaminophen in lactating women would be anticipated to be similar to that observed in non-pregnant women. Therefore, caution should be exercised when OFIRMEV is administered to a nursing woman.

8.4 Pediatric Use

Pediatric Use

OFIRMEV has been evaluated in a single intravenous dose of 15 mg/kg for the pediatric population of neonates (≥ 32 weeks post menstrual age) to adolescents. The mechanism of action of acetaminophen is similar to that observed in children age 2 years and older. Acetaminophen has an oral bioavailability of approximately 30% and a half-life of 2 hours. With single-dose administration of OFIRMEV in children and adolescents is similar to adults, but may differ in neonates due to immature hepatic and renal function. There are no studies of intravenous acetaminophen in neonates and infants. Dosing simulations from the published literature, acetaminophen has been reported to be excreted within 24 hours. In 101 patients with moderate to severe pain following total 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.

8.5 Geriatric Use

Geriatric Use

OFIRMEV has been evaluated in a single intravenous dose of 15 mg/kg for the pediatric population of neonates (≥ 32 weeks post menstrual age) to adolescents. The mechanism of action of acetaminophen is similar to that observed in children age 2 years and older. Acetaminophen has an oral bioavailability of approximately 30% and a half-life of 2 hours. With single-dose administration of OFIRMEV in children and adolescents is similar to adults, but may differ in neonates due to immature hepatic and renal function. There are no studies of intravenous acetaminophen in neonates and infants. Dosing simulations from the published literature, acetaminophen has been reported to be excreted within 24 hours.

8.6 Patients with Hepatic Impairment

OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should not be used in patients with hepatic impairment who have a history of acetaminophen hepatotoxicity. Acetaminophen has been observed to be increased in patients with chronic active liver disease (see Warnings and Precautions [7.1] and Precautions [7.2]). A reduced total daily dose of acetaminophen may be warranted.

8.7 Patients with Renal Impairment

OFIRMEV is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min), longer dosing intervals and reduced total daily dose of acetaminophen may be warranted.

10 OVERDOSAGE

In acute acetaminophen overdoses, dose-dependent, possibly fatal hepatic necrosis is the most prominent effect. Renal tubular necrosis, hydropic degeneration, and edema may also be present. Plasma glutamic oxaloacetic transaminase (SGOT) and plasma glutamic pyruvic transaminase (SGPT) may be increased. Plasma concentrations of glutamic oxaloacetic transaminase (SGOT) and plasma glutamic pyruvic transaminase (SGPT) are increased (2 to 10 times normal). Peripheral edema, anasarca, nausea, vomiting, diarrhea, hypotension, and respiratory depression, including convulsions and coma, may occur. Laboratory tests demonstrated changes rapid concomitantly with gluthathione and is then further metabolized to form cysteine and cysteine sulfenic acid.

Acetaminophen metabolism is mainly exceeded by the first-order kinetics in some patients who have been stabilized on hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

Inhibitor of the metabolism of acetaminophen.

Skin and subcutaneous tissue disorders: periorbital edema, rash, desquamation or erosion of the skin, bullae, eczema, dermatitis. Respiratory, thoracic and mediastinal disorders: pulmonary edema, cough, dyspnea, pleural effusion. Cardiac disorders: sinus tachycardia, reduced cardiac output, arrhythmias, pericardial effusion, conduction abnormalities, myocardial ischemia, necrosis, cardiomyopathy.

In a small number of patients with congenital malformations (1.3% to 2.4%) there was an increased incidence of abnormalities observed in the head and spine, including craniosynostosis, hypospadias, inguinal hernia, clubfoot, omphalocele, split-hand/split-foot, and cyclopia. In a small number of patients with congenital malformations (1.3% to 2.4%) there was an increased incidence of abnormalities observed in the head and spine, including craniosynostosis, hypospadias, inguinal hernia, clubfoot, omphalocele, split-hand/split-foot, and cyclopia.

There are no studies of intravenous acetaminophen in neonates and infants. Dosing simulations from the published literature, acetaminophen has been reported to be excreted within 24 hours. In 101 patients with moderate to severe pain following total 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.

8.2 Labor andDelivery

Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pulmonary infarction, shock, edema, and pleural effusion.

Skin and subcutaneous tissue disorders: petechiae, ecchymosis, papules, maculopapules, macules, urticaria, and angioedema.

Physical examination: elevated body temperature, tachycardia, tachypnea, leukocytes, and platelets may be increased. Laboratory tests demonstrated a decrease in platelet count and increased serum creatinine, bilirubin, and transaminase.

Adolescents

Children

Adults

The pharmacokinetic exposure of OFIRMEV observed in children is similar but increased significantly in neonates and infants. Dosing simulations from adults were used to predict the pharmacokinetic exposure of OFIRMEV observed in children based on an 80% higher body surface area compared to adults. In 101 patients with moderate to severe pain following total 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.

7.1 Effects of other Substances on Acetaminophen

Ethanol: Acetaminophen and ethanol are both metabolized by the enzymes of the cytochrome P450 system. Both ethanol and acetaminophen are metabolized by the enzyme CYP2E1 which 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, and the maximum hepatotoxic potential can only be approached if acetaminophen is consumed under medical supervision. Use of ethanol can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

7.2 Other Anticoagulants

Oxacillin sodium warfarin as an anticoagulant. As no studies have been performed in pregnant mice received oral acetaminophen at doses 0.3-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). 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).

8.8.4 Pediatric Use

Pediatric Use

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.

8.2 Labor and Delivery

In a small number of patients with congenital malformations (1.3% to 2.4%) there was an increased incidence of abnormalities observed in the head and spine, including craniosynostosis, hypospadias, inguinal hernia, clubfoot, omphalocele, split-hand/split-foot, and cyclopia.

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8.2 Labor and Delivery

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There are no studies of intravenous acetaminophen in neonates and infants. Dosing simulations from the published literature, acetaminophen has been reported to be excreted within 24 hours. In 101 patients with moderate to severe pain following total 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.

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