Indication: OFIRMEV (acetaminophen) injection is indicated for the
- Management of mild to moderate pain
- Management of moderate to severe pain with adjunctive opioid analgesics
- Reduction of fever

SPECIAL ADVERTISING SECTION
Funded by Cadence Pharmaceuticals, Inc.
In recent years there has been an increased awareness of the importance of pain management. The ten-year period that began January 1, 2001, was declared by Congress to be the Decade of Pain Control and Research. Even with this awareness and declaration, the management of acute pain remains inadequate, with many patients continuing to experience intense pain despite the availability of effective treatment options. Studies have demonstrated that the treatment of acute post-operative pain remains suboptimal.1,2 In 1995, Warfield and colleague conducted a national survey to assess the status of acute pain management in U.S. hospitals.1 The majority of the 500 patients surveyed (57%) who had surgery reported that their primary concern before surgery was the pain they might experience after the surgery. After surgery, 77% of the patients reported pain, with 80% of these patients reporting moderate to extreme pain. In 2003, Apfelbaum and colleagues conducted a national survey of 250 patients who underwent surgery.2 Their results were comparable to Warfield with the majority of patients, 82%, experiencing postoperative pain, and the majority, 86%, of these patients classifying their pain as being of moderate to severe intensity. Although 8 years passed between the surveys, the results illustrate the lack of progress in postoperative pain management.

Although opioids are the usual treatment for moderate to severe acute postoperative pain, their clinical effectiveness and usefulness are impeded by undesirable side effects.3 Side effects from opioid therapy such as nausea, vomiting, constipation, pruritus, and cognitive impairment impact pain therapy and are implicated in the continuing trend of under-treating postoperative pain.4 Many patients may decide to cope with their pain rather than be exposed to undesirable side effects.3

In 2001, The Joint Commission (TJC), formally known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), introduced standards that require healthcare organizations to make pain management a primary organizational priority and mandated pain assessment and treatment as part of routine patient care.5 According to TJC, the assessment, reassessment, and management of pain must be established as every patient’s right. Pain should not be permitted to interfere with patients’ optimal level of function and rehabilitation. Establishing and maintaining an institutional pain performance improvement plan is part of the TJC requirement.

Multimodal Pain Management

Because pain involves multiple mechanisms that rely on different receptor systems, it is beneficial to utilize a multimodal approach to achieve pain relief in the postoperative setting.6 The concept of multimodal analgesic therapy was introduced to provide effective postoperative pain relief, reduce opioid-related adverse effects, reduce surgical stress response and improve clinical outcomes by combining various analgesic techniques and different classes of drugs with varying mechanisms of action to achieve additive or synergistic effects.6,7 Multimodal analgesic regimens have demonstrated improved efficacy with improved tolerability.8-10 The multimodal pain management approach for acute pain utilizes a modification of the World Health Organization (WHO) Pain Relief Ladder.11,12 The WHO ladder illustrates the process of selecting drugs for specific types of pain based on the intensity of the pain. For moderate to severe pain intensity, opioids such as morphine, hydromorphone and oxycodone are added to non-opioid therapy.11 Multimodal pain treatment regimens are supported by numerous professional and regulatory organizations that have published guidelines for clinicians and institutions on the management of acute postoperative pain. The American Society of Anesthesiologists (ASA) published Practice Guidelines for Acute Pain Management in the Perioperative Setting in 2004.13 The ASA Task Force recommends that all surgical patients should receive an around-the-clock regimen of a non-opioid agent such as a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen.13,14 Supplemental regional anesthesia techniques may also be considered. These guidelines were recently reaffirmed in 2012.14

Multimodal Approach to Pain Management
Focus on OFIRMEV® (acetaminophen) Injection
Pain management has also become a priority for the reporting of patient satisfaction within hospitals. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey is the first national, standardized, publicly reported survey of patients’ perspectives of hospital care.15 HCAHPS, also known as the CAHPS® Hospital Survey, is a survey instrument and data collection methodology for measuring patients’ perceptions of their hospital experience. Public reporting information about patient experience of care allows for valid comparisons to be made across hospitals locally, regionally and nationally. The Centers for Medicare & Medicaid Services (CMS) implemented the HCAHPS survey in October 2006, and the first public reporting of HCAHPS results occurred in March 2008. Included in the HCAHPS survey are pain management questions.

**OFIRMEV: Mechanism, Indications, Dosage and Administration**

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent. Its chemical name is N-acetyl-p-aminophenol. The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not established, but is thought to primarily involve central actions.16 Potential analgesic mechanisms of acetaminophen have been described and include positive effects on the serotonergic descending inhibitory pathways and interactions with opioidergic systems, eicosanoid systems, and/or nitric oxide containing pathways.17 OFIRMEV is indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics and reduction of fever.16 OFIRMEV is approved for use in patients ≥ 2 years of age.16

IV acetaminophen is administered as a 15-minute infusion and may be given as a single or repeated dose for the treatment of acute pain or fever (TABLE 1). For adults and adolescents weighing ≥ 50 kg, the recommended dosage is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of 4000 mg per day. Dosing for children ≥ 2 years of age and adolescents and adults < 50 kg is listed in TABLE 1. For doses less than 1 gram, the appropriate dose must be withdrawn from the vial and placed into a separate container (eg, glass bottle, plastic intravenous container, or syringe) prior to administration. Once the vacuum seal of the glass OFIRMEV vial has been penetrated, or the contents transferred to another container, administer the dose within 6 hours.16

In order to prevent unintentional dosing of acetaminophen above the maximum daily dose in the hospital setting, with the addition of IV acetaminophen to the pain management armamentarium, all postoperative pain management hospital order sets should be reviewed. Doses of IV acetaminophen administered prior to or during surgery should be documented and readily available for review by nurses and pharmacists. Patients receiving IV acetaminophen 1 gram every 6 hours should not have another order for any acetaminophen-containing product on their medication profile. If a combination acetaminophen product is ordered for pain in addition to IV acetaminophen, the pharmacist should notify the prescriber and have the combination product re-timed to begin 4 to 6 hours after the last IV acetaminophen dose. The opioid within most combination products can be prescribed as a single agent for pain management if needed. If possible, an expert rule should be designed within a hospital’s computer program to quantify the amount of acetaminophen a patient receives in 24 hours.

Beginning in the Fall 2011, an initiative to help prevent patients from accidently exceeding the recommended dose of acetaminophen leading to potential liver failure was announced. The maximum daily dose of over-the-counter acetaminophen has been lowered from 4000 mg to 3000 mg.18 This change in maximum daily dose is listed in Table 1. For doses less than 1 gram, the appropriate dose must be withdrawn from the vial and placed into a separate container (eg, glass bottle, plastic intravenous container, or syringe) prior to administration. Once the vacuum seal of the glass OFIRMEV vial has been penetrated, or the contents transferred to another container, administer the dose within 6 hours.

**TABLE 1. Dosing of OFIRMEV for Adults, Adolescents, and Children ≥ 2 years old**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosing Interval</th>
<th>Maximum Single Dose</th>
<th>Maximum Total Daily Dose of Acetaminophen (by any route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥ 13 years old) ≥ 50 kg</td>
<td>Q6h</td>
<td>1000 mg (100 mL)*</td>
<td>4000 mg</td>
</tr>
<tr>
<td>Adults and adolescents (≥ 13 years old) &lt; 50 kg</td>
<td>Q6h</td>
<td>Weight-based dose 15 mg/kg†</td>
<td>75 mg/kg†</td>
</tr>
<tr>
<td>Children ≥ 2 to 12 years old</td>
<td>Q6h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Each mL contains 10 mg of OFIRMEV.
† Maximum daily dose up to 3750 mg.
• OFIRMEV is approved for use in patients ≥ 2 years of age.
• Minimum dosing interval is Q4h.
• For instructions regarding Q4h dosing, please see full Prescribing Information.

OFIRMEV® (acetaminophen) injection [Prescribing Information]. Cadence Pharmaceuticals, Inc.; San Diego, CA; 2010.
dose is for oral administration in an outpatient, uncontrolled setting. The approved dosing recommendation for OFIRMEV remains unchanged at 4000 mg per day for adults and adolescents weighing at least 50 kg.19

Metabolism, Pharmacodynamics and Pharmacokinetics of OFIRMEV

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 principle separate pathways: glucuronidation, sulfation, and oxidation.16 Unlike oral acetaminophen, IV acetaminophen does not undergo first-pass hepatic metabolism due to its direct systemic administration.16

IV acetaminophen acts rapidly, with onset of action 15 minutes after initiation of administration.20,21 The maximum concentration (Cmax) occurs at the end of the 15-minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the Cmax following OFIRMEV is up to 70% higher. Area under the concentration time curve is very similar for the same dose of OFIRMEV and oral acetaminophen.16 The peak effect occurs within one hour of administration and duration of effect is 4 to 6 hours.20,21

In an investigator-initiated study (funding provided by Cadence Pharmaceuticals), the plasma and CSF pharmacokinetics of oral, intravenous and rectal acetaminophen were compared.22 Six healthy male patients were included in a 3-way, crossover, single center, single-dose design pharmacokinetic study. There were three single dose daily treatment periods, each separated by an overnight washout period of 24 hours. Each treatment period consisted of administration of 1000 mg of acetaminophen IV or oral, or 1300 mg rectal. CSF and blood draws were performed just prior to study medication administration designated as T0 and at 8 additional specified time points in the next 6 hours. The IV route produced 76% higher mean plasma Cmax (P = 0.0004) than oral, and 256% higher Cmax (P < 0.0001) than rectal administration of acetaminophen (FIGURE 1). The median plasma Tmax for the IV route was earlier (0.25 hours) than the oral route (1 hour, P = 0.0018) or rectal route (2.5 hours, P = 0.0025). The mean CSF IV acetaminophen AUC over 6 hours was 75% higher than the oral AUC (P = 0.0099) and 142% higher than the rectal AUC (P = 0.0004). The mean CSF Cmax values for IV acetaminophen were 59.7% higher than oral (P < 0.0001) and 86.8% higher than rectal (P < 0.0001).

Figure 1a: Study of Acetaminophen Plasma Pharmacokinetics (IV, PO, PR)
Randomized, 3-way, cross-over design in 6 healthy volunteers; efficacy was not assessed

<table>
<thead>
<tr>
<th>Mean Plasma Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV acetaminophen 1 g</td>
</tr>
<tr>
<td>Oral acetaminophen 1 g</td>
</tr>
<tr>
<td>Rectal acetaminophen 1 g</td>
</tr>
</tbody>
</table>

- The IV route produced a 76% higher mean plasma Cmax than PO (P = 0.0004), and 256% higher than PR (P < 0.0001)
- The median plasma Tmax for the IV route was earlier (0.25h) than PO (1.0h, P = 0.0018) or PR (2.5h, P = 0.0025)

Note: PR acetaminophen data reflects standardization of the 1300 mg dose to 1000 mg (linear kinetics).

Data on file, Cadence Pharmaceuticals, Inc.

Figure 1b: Study of Acetaminophen Cerebrospinal Fluid PK (IV, PO, PR)
Randomized, 3-way, cross-over design in 6 healthy volunteers; efficacy was not assessed

<table>
<thead>
<tr>
<th>Mean Cerebrospinal Fluid Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV acetaminophen 1 g</td>
</tr>
<tr>
<td>Oral acetaminophen 1 g</td>
</tr>
<tr>
<td>Rectal acetaminophen 1 g</td>
</tr>
</tbody>
</table>

- The mean CSF IV acetaminophen AUC over 6h is 75% higher than the PO group (P = 0.0099) and 142% higher than the PR group (P = 0.0004)
- Comparing mean CSF Cmax values, the IV group was 59.7% higher than PO (P < 0.0001) and 86.8% higher than PR (P < 0.0001).
- The median CSF Tmax values were 2.0, 4.0 and 6.0h for IV, PO and PR, respectively.

*PR acetaminophen data reflects standardization of the 1300 mg dose to 1000 mg (linear kinetics).

Data on file, Cadence Pharmaceuticals, Inc.
Clinical Considerations
Regarding Route of Administration
Petring and colleagues demonstrated that gastric emptying is markedly delayed with the administration of morphine due to opioid-mediated mechanisms. Oral acetaminophen was used as a marker for gastric emptying and GI absorption.\(^{23}\)

In another clinical trial, surgical stress and opioid administration resulted in delayed and lower plasma concentrations of oral acetaminophen.\(^{24}\) Berger and colleagues demonstrated that oral acetaminophen, utilized as a marker for gastric absorption, was decreased after gastric administration on day 1 after cardiac surgery, mainly attributed to opioid-related gastric stasis.\(^{24}\)

Efficacy
The clinical efficacy of OFIRMEV for the management of postoperative pain is supported by the results of 2 pivotal clinical trials.\(^{20,25}\)

**Sinatra and Colleagues:** Sinatra and colleagues conducted a phase 3, randomized, double-blind, placebo-controlled, multi-dose study in total hip or total knee arthroplasty in 7 U.S. centers.\(^{20}\) One hundred one patients experiencing moderate to severe pain following total hip or knee replacement received either placebo or intravenous acetaminophen 1 gram. An additional 50 patients were treated with propacetamol (a pro-drug to acetaminophen). Data from these patients are not included because this drug is not approved for use in the U.S. Patients were started on trial medication on postoperative day 1 to allow for anesthesia washout and to ensure a stable baseline. Patients were allowed rescue medication with patient-controlled analgesia (PCA) morphine plus as-needed (PRN) bolus doses of morphine. Endpoints included: pain relief on a 5-point categorical scale; pain intensity; patient satisfaction; quantity of morphine consumed; and time to first use of rescue medication.\(^{20}\)

In the 6-hour, single-dose evaluation period, IV acetaminophen 1 gram plus PCA morphine demonstrated superior pain relief versus placebo plus PCA morphine (FIGURE 2). During the repeated-dose evaluation, the mean visual analog scale (VAS) pain intensity scores were significantly reduced in the IV acetaminophen group as compared with the placebo group (\(P < 0.01\)) at 24 hours. The time to first rescue medication was significantly longer (\(P < 0.001\)) for the IV acetaminophen group (median time to first rescue 3 hours) than for placebo (median time to first rescue 0.8 hours).

Morphine rescue consumption in the IV acetaminophen group was 46% lower (\(P < 0.01\)) after the first dose and 33% lower (\(P < 0.01\)) over 24 hours compared to placebo. The clinical benefit of reduced opioid consumption was not demonstrated. The patients’ global evaluation of satisfaction with study treatment after the initial dose and at 24 hours with repeated doses, were significantly higher (\(P < 0.01\)) for IV acetaminophen (79.6%) than for placebo (65.4%). Satisfaction was rated good to excellent on a 4-point categorical scale at 24 hours in 40.8% of the IV acetaminophen group and 23.1% in the placebo group. There were no significant differences between IV acetaminophen and placebo groups regarding the number of patients experiencing adverse events. No serious hepatic events were related to IV acetaminophen treatment. The most common adverse reactions reported with >5% incidence and higher than placebo were nausea, vomiting, enlarged abdomen, coughing, and pruritus.\(^{20}\)

**Wininger and Colleagues:** Wininger and colleagues conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled, repeated-dose, 24-hour study of the efficacy and safety of IV acetaminophen compared to placebo in abdominal laparoscopic surgery.\(^{25}\) Patients (N=244) received IV acetaminophen 1 gram or placebo every 6 hours, or IV acetaminophen 650 mg or placebo every 4 hours. IV or oral opioid rescue was available to all patients. The primary efficacy endpoint was the weighted sum of pain intensity differences over 24 hours (SPID24) based on VAS for the IV acetaminophen 1 gram every 6 hours group versus the placebo group. SPID24 for IV acetaminophen 650 mg every 4 hours versus placebo was a secondary end point. Additional endpoints included: patient satisfaction utilizing global evaluation of overall satisfaction; time to first rescue medication administration; and total amount of rescue medication consumption over 24 hours.

With regard to the primary endpoint measure, SPID24, the pain improvement results were statistically significant.
in favor of the IV acetaminophen 1 gram group compared with the placebo group ($P < 0.007$). With regard to the secondary endpoint, the total pain relief score from 1 hour to 24 hours (TOTPAR24; $P < 0.001$), sum of pain intensity differences over 6 hours (SPID6; $P < 0.001$), and total pain relief score from 1 hour to 6 hours (TOTPAR6; $P = 0.001$) were statistically significant in favor of the IV acetaminophen 1 gram group compared to the placebo group. The time to meaningful pain relief after the first dose was significantly shorter in patients who received IV acetaminophen 1 gram compared with patients in the placebo group ($P < 0.003$). Although the single-dose effects of IV acetaminophen 650 mg every 4 hours appeared to be less than those observed with IV acetaminophen 1 gram every 6 hours, the study was not powered for comparisons between the active-treatment groups and statistical analysis was not performed for the active-group comparisons. There was no statistically significant difference between the IV acetaminophen groups and the placebo group in the amount of rescue medication consumed in this study. Patient satisfaction with treatment was a pre-specified secondary endpoint where patients were asked to evaluate the study treatments overall using a 4-point categorical scale. The proportion of patients reporting good to excellent satisfaction after abdominal laparoscopic surgery was significantly higher in patients receiving IV acetaminophen 1 gram (86.9%) than in patients receiving placebo (70.3%; $P < 0.001$). The overall frequency of treatment emergent adverse effects across all the treatment groups was not significantly different. The most common adverse effects reported in > 10% of any group were constipation, flatulence, nausea, and headache.

_Aditional Clinical Trials:_ Acetaminophen injection has been studied in randomized clinical trials across a variety of surgical procedures including, but not limited to: orthopedic, gynecologic, general, otolaryngologic and cardiothoracic surgeries.$^{20,25,26-28}$ Clinical trials have demonstrated rapid and effective analgesia as measured by varying endpoints related to pain relief or reduction in pain intensity.

Memis and colleagues conducted a study to assess the analgesic efficacy, side effects, and time to extubation of intravenous paracetamol after major surgery in an intensive care unit.$^{26}$ Patients were randomized to receive intravenous paracetamol 1 gram every 6 hours or placebo in addition to intravenous meperidine as rescue. Behavioral pain scale and visual analog scores were significantly lower in the intravenous paracetamol group ($P < 0.01$). Postoperative rescue meperidine consumption was reduced by 61% over 24 hours in patients receiving IV paracetamol versus patients receiving placebo ($P < 0.05$).$^{26}$

A multi-center, double-blind, placebo-controlled study was conducted by Viscusi and colleagues in patients who underwent elective unilateral total hip arthroplasty. PCA was discontinued the morning following surgery. Patients were then randomized to receive a single dose of IV acetaminophen 1 gram or placebo when their pain was considered moderate to severe (100 mm VAS > 45 mm). The protocol specified opioid rescue analgesic as freely available. Primary efficacy outcomes include pain intensity difference from baseline at 1, 2, 3, and 4 hours post-dose. Secondary objectives were to determine the time and amount of opioid rescue used and to evaluate the safety of IV acetaminophen. IV acetaminophen demonstrated statistically significant improvement at all time intervals in pain intensity differences ($P < 0.001$ from 0.25 to 4 hours). Patients receiving IV acetaminophen 1 gram significantly ($P = 0.016$)

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**Figure 3: Reduced Opioid Consumption**

<table>
<thead>
<tr>
<th>Total Hip &amp; Knee Replacement¹</th>
<th>Major Abdominal Surgery²</th>
<th>Total Hip Replacement³ *</th>
<th>Adult Tonsillectomy⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Morphine over 24 h, mg)</td>
<td>(Meperidine over 24 h, mg)</td>
<td>(Morphine equivalents 0-6 h, mg)</td>
<td>(Meperidine doses over 24 h)</td>
</tr>
<tr>
<td>Placebo n=52</td>
<td>Placebo n=20</td>
<td>Placebo n=34</td>
<td>Placebo n=38</td>
</tr>
<tr>
<td>57.4</td>
<td>198</td>
<td>9.6</td>
<td>82</td>
</tr>
<tr>
<td>33% $P &lt; 0.01$</td>
<td>61% $P &lt; 0.05$</td>
<td>53% $P = 0.016$</td>
<td>78% $P &lt; 0.001$</td>
</tr>
<tr>
<td>OFIRMEV n=49</td>
<td>OFIRMEV n=20</td>
<td>OFIRMEV n=35</td>
<td>OFIRMEV n=38</td>
</tr>
<tr>
<td>38.3</td>
<td>77</td>
<td>4.5</td>
<td>18</td>
</tr>
</tbody>
</table>

_Note: Opioid consumption reduction is highly dependent on clinical trial design, and the clinical consequence of any amount of opioid consumption reduction may not have been evaluated or demonstrated in a given trial._

¹This study was terminated early due to the detection of particulates in some placebo vials

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reduced morphine consumption from 0 to 6 hours by 53% compared to placebo. This study was terminated early due to the detection of particulates in some placebo vials.

Atef and colleagues conducted a randomized, double-blind, prospective, placebo-controlled study comparing IV paracetamol 1 gram to placebo in patients undergoing elective standard bipolar diathermy tonsillectomy. After the surgeon had completed the tonsillectomy, patients received either placebo IV saline or paracetamol IV immediately after surgery and every 6 hours for a total of 4 doses. Pain intensity after surgery was measured using a 100 mm visual analog scale. The amount of rescue medication was also evaluated. The occurrence of insufficient pain relief was significantly greater in the patients receiving placebo than those receiving IV paracetamol ($P < 0.001$). There was reduced intramuscular (IM) meperidine consumption over 24 hours by 78% ($P < 0.001$) in patients receiving IV acetaminophen 1 gram compared to placebo.

FIGURE 3 summarizes the reduced opioid consumption in the trials described.

OFIRMEV Clinical Safety Profile
The safety of IV acetaminophen has been established with a clinical trial data set of 1020 adult patients, including 37.3% (n=380) who received 5 or more doses and 17% (n=173) who received more than 10 doses. The majority of adult patients, 86.9% (n=886) were treated with IV acetaminophen 1 gram every 6 hours. A total of 13.1% (n=134) received IV acetaminophen 650 mg every 4 hours. The most common treatment-emergent adverse events occurring in $\geq 3\%$ of adult patients treated with IV acetaminophen and at a greater frequency than placebo in repeated-dose studies were nausea, vomiting, headache, and insomnia (TABLE 2). The incidence of pyrexia was $5\%$ (n=22) for IV acetaminophen patients and $14\%$ (n=52) for placebo patients. Healthcare practitioners need to be aware that the antipyretic effects of IV acetaminophen may mask fever. IV acetaminophen was not associated with respiratory depression, sedation, postoperative ileus, cognitive impairment, upper gastrointestinal bleeding, surgical bleeding, renal toxicity, platelet dysfunction or cardiovascular thrombotic events.

Data from a pooled analysis of 5 repeated-dose placebo-controlled clinical studies involving adult patients demonstrated that the incidence of liver function enzyme elevations was comparable to that seen with placebo (TABLE 3).

**Table 2. Treatment-Emergent Adverse Events Occurring $\geq 3\%$ in Adults Receiving OFIRMEV and at a Greater Frequency Than Placebo in Repeated-Dose Studies**

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>OFIRMEV (N=402) n (%)</th>
<th>Placebo (N=379) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>138 (34%)</td>
<td>119 (31%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>62 (15%)</td>
<td>42 (11%)</td>
</tr>
<tr>
<td>Pyrexia†</td>
<td>22 (5%)</td>
<td>52 (14%)</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (10%)</td>
<td>33 (9%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 (7%)</td>
<td>21 (5%)</td>
</tr>
</tbody>
</table>

† Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

**Table 3. Hepatic Safety Data for OFIRMEV**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IV Acetaminophen (n=402)</th>
<th>Placebo (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3x ULN</td>
<td>1.1% (n=4)</td>
<td>1.7% (n=6)</td>
</tr>
<tr>
<td>&gt; 5x ULN</td>
<td>0.3% (n=1)</td>
<td>0.6% (n=2)</td>
</tr>
<tr>
<td>AST &gt; 3x ULN</td>
<td>1.0% (n=4)</td>
<td>1.1% (n=4)</td>
</tr>
<tr>
<td>&gt; 5x ULN</td>
<td>0.5% (n=2)</td>
<td>0.8% (n=3)</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

*Data from a pooled analysis of 5 repeated-dose placebo-controlled clinical studies involving adult patients.

**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**

2. OFIRMEV® (acetaminophen) injection [Prescribing Information]. Cadence Pharmaceuticals, Inc.; San Diego, CA; 2010.
PAIN MANAGEMENT: FOCUS ON OFIRMEV® (acetaminophen) INJECTION

Important OFIRMEV Safety Information

• OFIRMEV is contraindicated in patients with severe hepatic impairment, severe acute liver disease or with known hypersensitivity to acetaminophen or to any of the excipients in the formulation.

• Acetaminophen should be used with caution in patients with hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairments (CrCl ≤30 mL/min).

• Do not exceed the maximum recommended daily dose of acetaminophen. Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death.

• OFIRMEV should be administered only as a 15-min. infusion.

• Discontinue immediately if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with known acetaminophen allergy.

• The most common adverse reactions in adult patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia.

• The most common adverse reactions in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

• OFIRMEV is approved for use in patients ≥2 years of age.

• The antipyretic effects may mask fever in patients treated with OFIRMEV for postoperative pain.

Conclusion

The treatment of postoperative pain continues to be an unmet need for patients. Multimodal pain treatment regimens are supported by pain guidelines published by the ASA.

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

OFIRMEV is the only IV formulation of acetaminophen approved in the U.S. Integrating IV acetaminophen as part of postoperative multimodal analgesic regimens, as the foundational analgesic, may improve pain management, increase patient satisfaction with treatment and decrease opioid consumption.

REFERENCES


U.S. PHARMACIST APRIL 2012 8

Intravenous acetaminophen (paracetamol): comparable analgesic efficacy; better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. JAMA. 2005;293:120-127.


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)

DOSEAGE 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)

DOSEAGE 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)

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
intrahepatic 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: Lack of 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)

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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.

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.

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 dilation. 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

Table 1: Dosing for Adults and Adolescents

<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 any route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (13 years and older weighing ≤ 50 kg)</td>
<td>650 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
<td>4000 mg in 24 hours</td>
</tr>
<tr>
<td>Adults and adolescents (13 years and older weighing &gt; 50 kg)</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>
</tbody>
</table>

Revised: 11/2010
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>
<thead>
<tr>
<th>System Organ Class – Preferred Term</th>
<th>Treatment-Emergent Adverse Reactions occurring in ≥ 1% of OFIRMEV treated patients and having an incidence ≥ 3% and greater than Placebo (n=1020)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (4)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Psychiatric disorders ischemia</td>
</tr>
</tbody>
</table>

* 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).

- Blood and lymphatic system disorders: anemia
- 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, myalgia
- 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

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 Antiplatelets

OFIRMEV may cause an increase in INR in patients who have been stabilized on sodium warfarin as an antiplatelet. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral antiplatelet agents, 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 who were 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 small 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 (12.5)].

8.5 Geriatric Use
Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% percent 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

8.8 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 antipyreric and non-opiod analgesic agent. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular weight of 151.16. Its structural formula is:

\[ \text{HO-CH(NH\_2)-COOH} \]

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 cysteine hydrochloride, monohydrate, USP. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen and more than 90% is 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.

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.

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 (Cmax) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the Cmax following administration of OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

The pharmacokinetic parameters of OFIRMEV (AUC, Cmax, terminal elimination half-life [T1/2], 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>
<thead>
<tr>
<th>Subpopulations</th>
<th>Neonates</th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (mcg/mL)</td>
<td>62 (11)</td>
<td>28 (4)</td>
<td>29 (24)</td>
<td>29 (7)</td>
<td>28 (21)</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>25 (4)</td>
<td>4.2 (2.9)</td>
<td>3.0 (1.5)</td>
<td>2.9 (0.9)</td>
<td>2.4 (0.6)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>7.0 (2.7)</td>
<td>4.2 (2.9)</td>
<td>3.0 (1.5)</td>
<td>2.9 (0.9)</td>
<td>2.4 (0.6)</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.12 (0.04)</td>
<td>0.29 (0.15)</td>
<td>0.34 (0.10)</td>
<td>0.27 (0.08)</td>
<td>0.27 (0.08)</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>11 (2.2)</td>
<td>11 (2.2)</td>
<td>11 (2.3)</td>
<td>11 (2.3)</td>
<td>11 (2.3)</td>
</tr>
</tbody>
</table>

Table 3: OFIRMEV Pharmacokinetic Parameters
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 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.

**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.

OFIRMEV (acetaminophen) injection

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

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