Please see enclosed full Prescribing Information for OFIRMEV.
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1. EXECUTIVE SUMMARY

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

OFIRMEV is the first and only intravenous (IV) formulation of acetaminophen to be approved and marketed in the United States. The approval of OFIRMEV is supported by the results of 20 clinical trials involving 1375 patients. Three are pivotal studies. Two of these demonstrated the analgesic efficacy and safety of OFIRMEV in orthopedic and general surgeries. One demonstrated antipyretic efficacy and safety in adult patients.

In addition, there exists a considerable body of evidence supporting the efficacy of IV acetaminophen. In randomized, well-controlled clinical trials, IV acetaminophen has demonstrated effective pain relief in a wide variety of surgical procedures. In several of these studies, the inclusion of IV acetaminophen resulted in a statistically significant reduction in opioid consumption compared with placebo.

OFIRMEV has an established safety profile in adult and pediatric patients and was shown to be well tolerated in clinical trials. Since the introduction of IV acetaminophen in Europe in 2002, over 400 million doses have been distributed in over 60 countries worldwide.

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death.

Acetaminophen is contraindicated in patients with severe hepatic impairment, severe active liver disease, or with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation.

The IV form of acetaminophen may be particularly useful where rapid analgesia or fever reduction is clinically indicated, or where other routes of administration are impractical or undesirable.

Overview of Acute Pain and Current Medical Needs

Surgery is a common cause of acute pain and affects people of all ages. In 2006, 46 million surgical procedures were performed in the US. Although most surgical patients are assessed for postoperative pain and provided with management strategies, surveys have found that up to 80% of patients reported moderate to severe pain after surgery.

Even after a 1998 initiative by the Veterans Health Administration and a subsequent push by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to make pain the 5th vital sign, acute pain treatment after surgery is still not optimal. Thus, managing postoperative pain remains a challenge.

The American Society of Anesthesiologists (ASA) has developed practice guidelines to facilitate safe and effective acute pain management in the perioperative setting and recommends employing multimodal therapy as one method in the pursuit of these goals.
**Multimodal Therapy**

Acute pain, particularly postoperative pain, may be complex and multifactorial and may be optimally treated via a multimodal analgesic approach. In this form of therapy, two or more analgesics acting by different mechanisms are administered with the goal of providing analgesic efficacy superior to a single analgesic. This multimodal analgesic approach is already the standard of care for oral combination drugs—the most prescribed drugs in the US in 2009 were acetaminophen/opioid combinations such as Vicodin® (acetaminophen and hydrocodone bitartrate tablets).

The ASA guidelines support the concept of multimodal analgesia and encourage clinicians to employ multimodal pain management whenever possible in the perioperative setting. The guidelines recommend that all surgical patients receive an around-the-clock regimen of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or COX-2 inhibitors unless contraindicated and that “dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events.”

In practice, the multimodal strategy for the management of postoperative pain may involve a stepwise approach. (Figure 1A) Treatment begins at Step 1, with medications or interventions with different modes of action added in subsequent steps in response to increased pain intensity.

![Figure 1A. Multimodal Pain Management: Step Therapy](image)

Currently approved IV analgesic drug classes include opioids, NSAIDs, and acetaminophen. The ASA Task Force on Acute Pain Management “believes that NSAID, COXIB, or acetaminophen administration has a dose-sparing effect for systemically administered opioids.”

Adapted from Crews JC. *JAMA*. 2002;288:629-632.
Multimodal Therapy: Potential Benefits of OFIRMEV

A potential benefit of using nonopioid analgesics such as OFIRMEV as part of a multimodal regimen is the achievement of clinically significant pain relief while reducing the consumption of opioids.1-5

As the only IV formulation of acetaminophen available in the US, OFIRMEV provides the only option to use IV acetaminophen as part of a multimodal regimen.

OFIRMEV may fill a medical need for a well-tolerated and effective analgesic regimen in the perioperative setting. With limited IV analgesic options to manage acute pain in a multimodal fashion, an agent that has demonstrated safety and efficacy in the treatment of pain is highly desirable.

Another potential benefit of OFIRMEV is its well-established safety profile: OFIRMEV is not associated with adverse reactions such as respiratory depression, postoperative ileus, sedation, cognitive impairment in older patients, upper gastrointestinal bleeding, surgical site bleeding, renal toxicity, platelet inhibition, and cardiovascular thrombotic events. Nor does it carry boxed warnings for cardiovascular, renal, or gastrointestinal adverse effects.1

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.1

OFIRMEV is contraindicated in patients with severe hepatic impairment, severe active 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 the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.1

Overview of the Treatment of Fever and Current Medical Needs in Adults

Fever is an elevation in body temperature and is commonly defined as a body temperature greater than 100.4 °F (38 °C).12-14 Fever can have both infectious (bacterial, viral) and noninfectious (inflammation, drug hypersensitivity) etiologies.15 High fever may result in alterations of mental status, confusion, irritability, or convulsions.16

The availability of an IV formulation may address a significant and long-standing unmet medical need for rapid and reliable delivery of acetaminophen for fever reduction where other routes of administration are impractical.
Pain, Fever, and Current Medical Needs in Children

At the recommended therapeutic dosing, acetaminophen has a demonstrated and well-established safety profile and has been an effective analgesic and antipyretic for over 50 years in children. Despite the widespread use of acetaminophen, oral or rectal delivery is not always ideal for hospitalized children. Oral administration may not be practical in patients who are anesthetized or nil per os (NPO) following surgery and may be an impractical route in some pediatric patients. Rectally administered acetaminophen can be difficult to administer for the healthcare professional and unpleasant for the patient.

Fever is one of the most common reasons parents bring their children to the emergency room for evaluation and treatment. Up to 4% of children experience fever-induced seizures, or febrile seizures, and up to 17% of children who were preterm births may suffer febrile seizures. IV NSAIDs such as ibuprofen and ketorolac are not approved for use in children for fever reduction.

IV Acetaminophen Development

An IV formulation of acetaminophen was first approved in 2001 for use in France and has been marketed in many countries as Perfalgan® by Bristol-Myers Squibb Company (BMS) since 2002. Currently, IV acetaminophen is approved in more than 60 countries. The safety of IV acetaminophen has been monitored through a postmarketing surveillance program with more than 400 million units distributed since its European approval. Additionally, the results of many randomized controlled trials (RCTs) evaluating IV acetaminophen for the management of pain or fever have been published in peer-reviewed literature.

In 2006, Cadence licensed North American development and commercialization rights to IV acetaminophen from BMS and undertook its US development. The clinical development program was completed in 2008 and included 20 trials involving 1375 patients. OFIRMEV was approved by the Food and Drug Administration on November 2, 2010, for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever.
2. PRODUCT DESCRIPTION

OFIRMEV (acetaminophen) injection is a nonsalicylate antipyretic and nonopioid analgesic agent. It is distinct from other commonly used drugs to reduce fever and pain, such as NSAIDs, as it is not a significant direct COX inhibitor; therefore, OFIRMEV is in a different drug class with a different mechanism of action. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen is the US adopted name for the compound, which is known by its nonproprietary name of paracetamol outside the US.

Acetaminophen has a molecular weight of 151.16. Its structural formula is:

![Acetaminophen Structural Formula]

OFIRMEV injection is a sterile, clear, colorless, nonpyrogenic, isotonic formulation of acetaminophen intended for IV infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP; 3850 mg mannitol, USP; 25 mg cysteine hydrochloride, monohydrate, USP; and 10.4 mg dibasic sodium phosphate, anhydrous, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

In general, acetaminophen is poorly soluble in solution. In addition, acetaminophen is highly reactive with oxygen and rapidly polymerizes in the presence of oxygen. The unique formulation and manufacturing process for OFIRMEV has finally created a stable liquid solution of acetaminophen suitable for direct intravenous administration.

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
- Reduction of fever
4. CLINICAL PHARMACOLOGY

Pharmacology Overview
Acetaminophen exerts analgesic and antipyretic effects following systemic administration. Onset of analgesia occurs within the first 15 minutes of administration of OFIRMEV. Peak analgesic effect occurs within 1 hour, and the duration of analgesic effect is throughout 6 hours.\(^1\)\(^2\) Fever is reduced within 30 minutes after the start of the infusion, and the duration of antipyretic effect is through 6 hours.\(^2\)

Pharmacokinetics (PK) of OFIRMEV has been studied in patients and healthy subjects, from premature neonates up to adults 60 years of age.\(^1\)

The \(C_{\text{max}}\) occurs at the end of the 15-minute infusion of OFIRMEV. The PK profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.\(^1\)

Distribution
At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%).\(^1\) Acetaminophen appears to be widely distributed throughout most body tissues except fat and rapidly enters the CNS in a concentration (\(C_{\text{max}}\))–driven process.\(^1\)\(^2\)

The PK exposure of OFIRMEV observed in children and adolescents is similar to adults but is higher in neonates and infants.\(^1\) (Table 4A)

PK parameters of OFIRMEV (AUC, \(C_{\text{max}}\), terminal elimination half-life [\(T_{1/2}\)], systemic clearance [CL], and volume of distribution at steady state [\(V_{ss}\)]) following administration of a single IV dose of 15 mg/kg for the pediatric population and 1000 mg in adults are summarized in Table 4A.
Table 4A. Pharmacokinetic Parameters of OFIRMEV1

<table>
<thead>
<tr>
<th>Subpopulations</th>
<th>AUC (µg × h/mL)</th>
<th>Cmax (µg/mL)</th>
<th>Mean (SD)</th>
<th>CL (L/h/kg)</th>
<th>Vss (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>62 (11)</td>
<td>25 (4)</td>
<td>7.0 (2.7)</td>
<td>0.12 (0.04)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>Infants</td>
<td>57 (54)</td>
<td>29 (24)</td>
<td>4.2 (2.9)</td>
<td>0.29 (0.15)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Children</td>
<td>38 (8)</td>
<td>29 (7)</td>
<td>3.0 (1.5)</td>
<td>0.34 (0.10)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>41 (7)</td>
<td>31 (9)</td>
<td>2.9 (0.7)</td>
<td>0.29 (0.08)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Adults</td>
<td>43 (11)</td>
<td>28 (21)</td>
<td>2.4 (0.6)</td>
<td>0.27 (0.08)</td>
<td>0.8 (0.2)</td>
</tr>
</tbody>
</table>

AUC=area under the concentration vs time curve; Cmax=maximum concentration; T1/2=elimination half-life; CL=clearance; Vss=volume of distribution at steady state.

These PK parameters for adults, adolescents, and children are achievable by delivering dosages as described in Section 7 of this Monograph. The PK exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from PK 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 PK exposure similar to that observed in children 2 years and older.1

Pediatric Pharmacokinetics

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 (n=225) clinical trials, including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses.1

A meta-analysis of pediatric PK data allowed the creation of a maturational PK model for acetaminophen.2 A pattern between normalized acetaminophen clearance (CL) adjusted for body weight and age (expressed as PMA) was observed, with a rapid increase in CL in neonates and infants.2 (Figure 4A)
Acetaminophen PK and exposure levels following single and multiple doses of OFIRMEV 15 mg/kg Q6h in children and adolescents were comparable to the normalized values in adults.²
Metabolism

Acetaminophen metabolism is well characterized. Unlike oral acetaminophen, IV acetaminophen does not undergo first-pass hepatic metabolism due to its direct systemic administration. In adults and children, acetaminophen is metabolized by the liver via 3 major pathways: glucuronidation (50% to 60%), sulfation (25% to 35%), and oxidation (<10%). In neonates and infants, sulfation is the predominant metabolic pathway due to delayed maturity in glucuronidation. Other minor acetaminophen metabolic pathways include hydroxylation, methoxylation, and hydrolysis.

Within therapeutic doses of acetaminophen, small amounts of $N$-acetyl-$p$-benzoquinone imine (NAPQI), a toxic intermediate, are produced primarily by cytochrome (CYP) P450 enzyme CYP2E1. NAPQI is then conjugated with intracellular glutathione to produce a nontoxic thiol metabolite and is excreted in the urine. At very high acetaminophen dose levels or in the presence of significant depletion of glutathione stores, NAPQI is produced in larger amounts, which can result in hepatotoxicity.

These major metabolic pathways and the chemical structures of the metabolites are shown schematically in Figure 4B.

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**Figure 4B. Metabolism of Acetaminophen in Humans**

Clearance

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen, and more than 90% of the administered dose is excreted within 24 hours.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.¹

Pharmacokinetic Parameters of OFIRMEV and Oral Acetaminophen

An open-label, 4-period, randomized, crossover study was designed to compare the PK, pharmacodynamics, and safety of OFIRMEV 1 g and oral acetaminophen (rapid-release liquid formulation) administered Q4h (to a daily maximum of 4000 mg) or Q6h over a 48-hour treatment period (8 doses were administered on each schedule). Thirty-two healthy adult males completed the study. The subjects ranged in age from 18 to 48 years with a mean age of 29.2 years.²

Mean acetaminophen concentration-time profiles for Q6h dosing are shown in Figure 4C.² An assessment of the mean trough plasma acetaminophen levels prior to Doses 2 through 8 and the plasma levels following Day 2, Dose 4 (last or 8th dose), in comparison to the values following the first dose, did not demonstrate any additional accumulation beyond 12 hours through to the end of the 48-hour study period.²
OFIRMEV administration resulted in an approximately 70% higher $C_{max}$ with the time to reach maximum concentration ($T_{max}$) approximately 30 minutes earlier compared to the oral acetaminophen formulation. Note that the OFIRMEV $T_{max}$ occurred at the end of the 15-minute infusion. The higher $C_{max}$ with OFIRMEV did not result in clinically meaningful differences in the adverse reactions or the relative levels of glutathione conjugates compared with the rapid-release oral liquid acetaminophen. Distribution and mean CL values at steady state are comparable between delivery methods, and neither the route of administration nor the dosing interval had a clinically significant impact on fractional excretion in urine of free or unconjugated acetaminophen. The half-lives ($t_{1/2}$) were also found to be comparable (2.39 hours for OFIRMEV vs 2.66 hours for oral acetaminophen). Adverse reactions, drug accumulation, effects on platelet aggregation, and changes in electrocardiograms were comparable between IV and oral dosing.

In a separate multicenter, double-blind, randomized, placebo-controlled study that evaluated patients who received elective unilateral total hip arthroplasty, the PK parameters were comparable to those of the healthy adult subjects in prior research.
Pharmacodynamics

Acetaminophen penetrates readily through an intact blood-brain barrier and enters the CNS rapidly in a C<sub>max</sub>–driven process.<sup>2</sup> Levels are detectable in the CSF within 5 minutes after OFIRMEV injection.<sup>31</sup> Given that the mechanism of action of acetaminophen is thought to be centrally mediated, the earlier peak CSF levels may correlate with the more rapid onset of action.<sup>2</sup>

5. CLINICAL EFFICACY

The efficacy of OFIRMEV for the management of pain and fever is supported by 3 pivotal, well-controlled clinical trials.<sup>2</sup> In addition, several other trials have examined the analgesic efficacy of IV acetaminophen. Procedure types included, but were not limited to, orthopedic surgery (including total hip or knee replacement); gynecologic surgery; general surgery; ear, nose, and throat (ENT) surgery; and cardiothoracic surgery.<sup>2-5,32</sup> Across this extensive clinical data set, IV acetaminophen showed a significant and reproducible benefit in analgesia as measured by a variety of endpoints relating to pain relief or reduction in pain intensity. Importantly, several studies demonstrated that including IV acetaminophen in the analgesic regimen resulted in significant reductions in opioid consumption.<sup>2-5</sup> The clinical benefit of reduced opioid consumption was not demonstrated.

Acetaminophen is contraindicated in patients with severe hepatic impairment, severe active liver disease or with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation.<sup>1</sup>

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.<sup>1</sup>
Analgesic Efficacy in Orthopedic Surgery

Sinatra et al (Pain Study 1): A phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated the analgesic efficacy and safety of single and repeated doses of OFIRMEV 1 g in comparison with placebo in 101 patients experiencing moderate to severe pain following total hip or knee replacement.* Patients were allowed rescue medication with patient-controlled analgesia (PCA) morphine. Efficacy was measured as:

- Pain relief on a 5-point verbal scale at selected intervals up to 6 h (primary endpoint)
- Pain intensity on a 100-mm visual analog scale and a 4-point verbal scale at selected intervals over 24 h†
- Quantity of morphine consumed
- Time to first use of rescue medication
- Patients’ global evaluation of satisfaction at 24 h

Pain Relief and Pain Intensity

In a 6-h, single-dose evaluation period, OFIRMEV 1 g + PCA morphine demonstrated superior pain relief vs placebo + PCA morphine (15 minutes through 6 h, \( P<0.05 \)).† (Figure 5A) In a repeated-dose evaluation period, OFIRMEV showed a greater reduction in pain intensity over 24 h (SPID24) compared to placebo (\( P<0.001 \)).

Figure 5A. Mean Pain Relief (Total Hip or Knee Replacement)\

\( \text{OFIRMEV 1 g + PCA morphine (n=49)} \)
\( \text{Placebo + PCA morphine (n=52)} \)
\( P<0.05 \)

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.

*This study also included an active comparator, propacetamol. However, since propacetamol is not commercially available in the United States, the data here reflect only IV acetaminophen and placebo. Therefore, for discussion purposes, propacetamol is not included. In total, 49 patients received IV acetaminophen, 52 received placebo, and 50 received propacetamol.
†Since this study was completed, the preferred primary efficacy endpoints for regulatory evaluations of pivotal studies in pain indications has shifted to a summed difference in pain intensity. An extended analysis was performed in order to confirm and augment the statistically significant single- and repeated-dose efficacy endpoints in favor of OFIRMEV vs placebo observed in this trial.
Morphine Consumption

OFIRMEV 1 g + PCA morphine significantly reduced morphine consumption vs placebo + PCA morphine alone (−46% after first dose, *P* <0.01; −33% over 24 h, *P* <0.01). (Figure 5B) Median time to first rescue medication was significantly longer with OFIRMEV 1 g compared with placebo (3 h vs 0.8 h, *P*=0.0001). The clinical benefit of reduced opioid consumption was not demonstrated.

Figure 5B. Reduction in Morphine Consumption (Total Hip or Knee Replacement Surgery)³

![Graph showing morphine consumption reduction](image)

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.

Patient Satisfaction

Patients’ global evaluation of study treatment (excellent plus good scores) significantly favored the OFIRMEV group over PCA morphine alone (40.8% vs 23.1%, *P*=0.004).²,³ (Figure 5C)
Figure 5C. Patient-Reported Satisfaction With Study Treatment at 24 h*  
(Total Hip or Knee Replacement)**

<table>
<thead>
<tr>
<th>Placebo (n=52)</th>
<th>OFIRMEV 1 g (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.1%</td>
<td>40.8% P=0.004†</td>
</tr>
</tbody>
</table>

Excellent + good

There were no differences between OFIRMEV and placebo groups in incidence of adverse events. No serious hepatic events were related to treatment with OFIRMEV 1 g.2

The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients.1

Analgesic Efficacy in General Surgery

Data on file (Pain Study 2): A phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group, repeated-dose study of the analgesic efficacy and safety of OFIRMEV vs placebo for the treatment of postoperative pain after abdominal laparoscopic surgery. Patients (N=244) received OFIRMEV 1 g or placebo Q6h, or OFIRMEV 650 mg or placebo Q4h. Opioid rescue medication was available to all patients. Efficacy measures included:

- OFIRMEV 1 g Q6h vs combined placebo group: sum of pain intensity differences from baseline (based on VAS score) over 24 h (primary endpoint)
- OFIRMEV 650 mg Q4h vs the combined placebo group: sum of pain intensity differences from baseline (based on VAS score) over 24 h
- Subjects’ global evaluations of study treatment at 24 h
- Time to first rescue medication administration
- Total amount of rescue medication consumption over 24 h

*Subjects were asked to evaluate the study treatments, overall, using a 4-point categorical scale.
†Overall P value derived from a statistical analysis of a 4-point categorical scale.
Pain Intensity
A significantly greater reduction in pain intensity differences from baseline was seen with OFIRMEV 1 g compared to the combined placebo group over the 24-hour period \( (P=0.0068) \). (Figure 5D)

Time to meaningful pain relief after the first dose was significantly shorter in subjects who received OFIRMEV 1 g compared to the matched placebo group, with median values of 24.9 minutes and 53.9 minutes, respectively \( (P=0.0028) \).2

![Figure 5D. Mean Reduction in Pain Intensity Differences From Baseline Over 24 h (Abdominal Laparoscopy)](image)

Data on file (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).

Similarly, there was a significant difference in pain intensity differences from baseline seen with OFIRMEV 650 mg compared with the combined placebo group over 24 h \( (P=0.0183) \).2

Morphine Consumption
No statistical differences were found between OFIRMEV 1 g or 650 mg and the combined placebo groups in total rescue medication consumption or in the first time to rescue medication.2
**Patient Satisfaction**

Patient global evaluation of study treatment (excellent plus good scores) significantly favored OFIRMEV 1 g over the control group ($P=0.0004$).\(^2\) (Figure 5E)

*Figure 5E. Patient-Reported Satisfaction With Study Treatment at 24 h* *(Abdominal Laparoscopy)*\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=108)</th>
<th>OFIRMEV 1 g (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent + good</td>
<td>70.3%</td>
<td>86.9%</td>
</tr>
</tbody>
</table>

Data on file (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).

Do not exceed the maximum recommended daily dose of acetaminophen.\(^1\)

**Additional Randomized Controlled Trials**

Including the pivotal studies discussed above, a number of RCTs evaluated the efficacy of IV acetaminophen and support its use in a variety of surgeries and pain severities. These studies involved outpatients and inpatients, from relatively healthy adults undergoing minor surgery to the elderly and medically compromised patients undergoing major surgery. Though trial design and endpoints varied, IV acetaminophen, either alone (mild to moderate pain) or as part of a multimodal analgesic regimen with adjunctive opioids (moderate to severe pain), has consistently demonstrated analgesic efficacy in many different pain models.\(^2\)

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\(^1\)Subjects were asked to evaluate the study treatments, overall, using a 4-point categorical scale.

\(^2\)Overall $P$ value derived from a statistical analysis of a 4-point categorical scale.
Opioid Consumption

Reduced opioid consumption with IV acetaminophen has been demonstrated in a number of trials across a variety of surgical procedures including total hip or knee replacement, tonsillectomy, and abdominal surgeries, with significant reductions compared to placebo.2-5 In total hip or knee replacement, median time to first rescue medication was significantly longer with IV acetaminophen 1 g compared with placebo (3 h vs 0.8 h, \( P=0.0001 \)).3 In adult tonsillectomy, significantly more patients receiving acetaminophen 1 g did not require any opioids (71%) compared with those in the placebo group (0%).4 In abdominal surgery, opioid consumption was significantly less in the IV acetaminophen plus IV meperidine group compared to the placebo plus IV meperidine group (77 mg vs 198 mg, \( P<0.05 \)).5 While IV acetaminophen has demonstrated the ability to reduce opioid consumption, the clinical significance has not been established.

Patient Satisfaction

Patient reports of global satisfaction in a number of trials, across a variety of surgeries, have been shown to favor IV acetaminophen over placebo. The greatest differences between IV acetaminophen and placebo groups, as measured by the percentage of patients reporting good or excellent satisfaction, were demonstrated in orthopedic and general surgeries.2,3

The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients.1

Acetaminophen is contraindicated in patients with severe hepatic impairment, severe active liver disease or with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation.1

Antipyretic Efficacy

Royal et al: A phase 3, randomized, double-blind, placebo-controlled, single-center study that evaluated the antipyretic efficacy and safety of a single dose of OFIRMEV 1 g compared with placebo in 60 healthy adult males who developed fever induced by a standard dose of endotoxin.2

OFIRMEV 1 g was shown to be effective in blunting the peak temperature produced by endotoxin and reducing the fever it produced for a period of up to 6 h. The weighted sum of temperature differences over 6 h (primary endpoint) was significantly better for OFIRMEV 1 g vs placebo (\( P=0.0001 \)).2 (Table 5A)
Importantly, OFIRMEV 1 g demonstrated a rapid onset of action and showed statistically significant temperature differences from baseline vs placebo at T30 minutes (15 minutes after completing the infusion) \((P=0.0085)\). Statistically significant reductions in temperature at each time point from 30 minutes through 5.5 h were also observed for subjects who received OFIRMEV 1 g vs placebo.\(^2\) (Figure 5F)

![Figure 5F. Mean Body Temperature Over Time: OFIRMEV 1 g vs Placebo\(^2\)](image)

\(\text{Data on file}\)

Randomized, double-blind, placebo-controlled clinical trial comparing a single dose of OFIRMEV 1 g and placebo in 60 healthy adult males with endotoxin-induced fever. Primary endpoint: weighted sum of temperature differences.

---

### Table 5A. Weighted Sum of Temperature Differences From Baseline (T0) Through T6 h\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>OFIRMEV 1 g (n=31)</th>
<th>Placebo (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (°C)</td>
<td>−3.7</td>
<td>−0.7</td>
</tr>
<tr>
<td>Median (°C)</td>
<td>−3.7</td>
<td>−1.2</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>(P=0.0001)</td>
</tr>
</tbody>
</table>
6. **CLINICAL SAFETY**

The safety of OFIRMEV has been established by an extensive clinical trial data set comprising 1020 adult patients who 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 adult patients were treated with OFIRMEV 1 g Q6h. A total of 13.1% (n=134) received OFIRMEV 650 mg Q4h. 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 (n=225) clinical trials, 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 a Q4h, Q6h, or Q8h schedule.¹ ²

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.¹

**Hepatotoxicity in Clinical Trials**

Within therapeutic dosing, data demonstrate that the incidence of liver elevations during treatment was comparable to placebo.² (Table 6A) Hospitalization may be a contributing factor in low-level LFT elevations (<3× ULN).³³ These are not reflective of significant hepatic compromise, but represent typical mild perturbations that commonly occur postanesthesia and postsurgery.³⁴-³⁷

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

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

Hepatotoxicity was also assessed using Hy’s law analysis. Hy’s law states that the combination of elevated bilirubin and transaminase levels results in at least a 10% chance of severe liver injury and was incorporated in the FDA’s July 2009 Guidance for Industry—Drug-Induced Liver Injury: Premarketing Clinical Evaluation.³⁸,³⁹
Using the data from the OFIRMEV clinical development program, a scatterplot of peak ALT vs peak total bilirubin (TBL) values for the OFIRMEV Adult Placebo-Controlled Safety Population (N=1329) was generated. (Figure 6A) This study pool included single- and repeated-dose, placebo-controlled studies. The distribution of these TBL and ALT postbaseline values shows a similar overlap between OFIRMEV (n=824) and placebo (n=505) groups. Note also that there were no Hy’s law cases (as defined by 2 × TBL and 3 × ALT values above baseline with no other known causes) seen in this study pool. Based on these data, there was no evidence of a serious drug-induced hepatotoxicity signal during the OFIRMEV clinical development program.2

Figure 6A. Scatterplot of Peak ALT vs Peak TBL Values (All-Adult Placebo-Controlled Patient Studies Pool [OFIRMEV Safety Population])

ALT=alanine aminotransferase; ULNR=upper limit normal range.
Hepatotoxicity in Clinical Use

From the time IV acetaminophen was first marketed (as Perfalgan®) in 2002 through 2010, over 400 million units were distributed for use, and approximately 65 million patients had been treated. The incidence of hepatic-related adverse events noted in postmarketing surveillance reports are summarized in Table 6B.2

The 8-year data showed 212 reports of medically significant hepatic adverse events associated with IV acetaminophen without regard to causality assessment. Among 21 fatalities reported, 15 were considered possibly related to IV acetaminophen use through a temporal association. The analysis found that other etiologies also were present. There were a total of 44 cases in which there was some evidence of drug-induced liver injury (DILI). But in the majority of these, the data were considered incomplete for evaluation of the role of acetaminophen. A total of 8 cases of DILI were fatal, of which 3 were assessed as related to acetaminophen exposure and 5 were considered possibly related to acetaminophen only due to a temporal association. In each of these cases, there were other etiologies present that may have caused or contributed to the hepatic events. Six of the suspect cases of DILI were reported as having received doses in excess of the recommended dosing regimens in the Bristol-Myers Squibb Company core data sheet, either as IV acetaminophen alone or in combination with oral acetaminophen or IV propacetamol.*2

<table>
<thead>
<tr>
<th>Hepatic Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total medically significant hepatic adverse events</td>
<td>0.0003%</td>
</tr>
<tr>
<td>Fatal events</td>
<td>0.00003%</td>
</tr>
<tr>
<td>Drug-induced liver injury (DILI)</td>
<td>0.00006%</td>
</tr>
</tbody>
</table>

Contraindications

OFIRMEV is contraindicated1:

- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation
- In patients with severe hepatic impairment or severe active liver disease

* Propacetamol is not commercially available in the United States.
Warnings and Precautions

Hepatic Injury
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. Do not exceed the maximum recommended daily dose of acetaminophen.1

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia (eg, due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤30 mL/min).1

Allergy and Hypersensitivity
There have been postmarketing 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.1

Adverse Reactions

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.1

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 Q6h. A total of 13.1% (n=134) received OFIRMEV 650 mg Q4h.1

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 6C. The most common adverse reactions in adult patients treated with OFIRMEV (incidence ≥5% and greater than placebo) were nausea, vomiting, headache, and insomnia.1
Table 6C. Treatment-Emergent Adverse Reactions Occurring in ≥3% of Patients Receiving OFIRMEV and at a Greater Frequency Than Placebo in Placebo-Controlled, Repeated-Dose Studies

<table>
<thead>
<tr>
<th>System Organ Class—Preferred Term</th>
<th>OFIRMEV (n=402) n (%)</th>
<th>Placebo (n=379) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<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>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>22 (5)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>39 (10)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 (7)</td>
<td>21 (5)</td>
</tr>
</tbody>
</table>

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 disorders 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, trismus); psychiatric disorders (anxiety); respiratory, thoracic, and mediastinal disorders (dyspnea); and 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 (n=225) clinical trials, 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 a Q4h, Q6h, or Q8h 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.

*Pyrexia adverse reaction frequency data are included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.
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, peripheral edema, pyrexia); investigations (hepatic enzyme increase); metabolism and nutrition disorders (hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia); musculoskeletal and connective tissue disorders (muscle spasm, pain in extremity); nervous system disorders (headache); psychiatric disorders (insomnia); renal and urinary disorders (oliguria); respiratory, thoracic, and mediastinal disorders (pulmonary edema, hypoxia, pleural effusion, stridor, wheezing); skin and subcutaneous tissue disorders (periorbital edema, rash); vascular disorders (hypertension, hypotension).1

Use in Specific Populations

Pregnancy

Pregnancy Category C. There are no studies of IV 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.1 The results from a large population-based prospective cohort, including data from 26,424 women with live-born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.1 While animal reproduction studies have not been conducted with IV 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 g/day, based on body surface area) 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 body surface 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.1
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 postweaning 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.¹

**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.¹

**Nursing Mothers**
While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1%–2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Caution should be exercised when OFIRMEV is administered to a nursing woman.¹

**Pediatric Use**
The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ≥2 years old is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and PK data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥32 weeks postmenstrual 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.¹

**Geriatric Use**
Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 years and over, while 5% were age 75 years 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.¹
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. A reduced total daily dose of acetaminophen may be warranted.¹

Patients With Renal Impairment

In cases of severe renal impairment (creatinine CL ≤30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.¹

Drug Interactions

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.¹

Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.¹

7. DOSING

OFIRMEV 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 7A) No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents. The maximum daily dose of acetaminophen is based on all routes of administration (ie, intravenous, oral, and rectal) and all products containing acetaminophen.¹
Adults and Adolescents (≥13 Years Old)

Adults and adolescents weighing ≥50 kg: the recommended dosage of OFIRMEV is 1000 mg Q6h or 650 mg Q4h, 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.\(^1\)

Adults and adolescents weighing <50 kg: the recommended dosage of OFIRMEV is 15 mg/kg Q6h or 12.5 mg/kg Q4h, 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.\(^1\)

Children ≥2 Years Old

Children ≥2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg Q6h or 12.5 mg/kg Q4h, 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.\(^1\)

**Table 7A. Recommended Dosing of OFIRMEV for Adults, Adolescents, and Children ≥2 Years Old\(^1\)**

<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 h</td>
</tr>
<tr>
<td>Adults and adolescents (13 years and older) weighing &lt;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 h (up to 3750 mg)</td>
</tr>
<tr>
<td>Children ≥2 to 12 years old</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 h (up to 3750 mg)</td>
</tr>
</tbody>
</table>
8. **ADMINISTRATION**

**Instructions for IV Administration**

For adult and adolescent patients weighing ≥50 kg requiring 1000-mg doses of OFIRMEV, administer the dose by inserting a vented IV set through the septum of the 100-mL vial. OFIRMEV may be administered without further dilution. Examine the vial contents before dose preparation or administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15 minutes. Use aseptic technique when preparing OFIRMEV for intravenous infusion. Do not add other medications to the OFIRMEV vial or infusion device.¹

**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 IV infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100-mL vial of OFIRMEV is not intended for use in patients weighing <50 kg. OFIRMEV is a single-use vial, and the unused portion must be discarded.¹

Place small-volume pediatric doses, up to 60 mL in volume, in a syringe and administer over 15 minutes using a syringe pump.¹

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.¹

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.¹

Do not add other medications to the OFIRMEV solution. Diazepam and chlorpromazine hydrochloride are physically incompatible with OFIRMEV, therefore do not administer simultaneously.¹

**Storage and Handling**

OFIRMEV is supplied in a 100-mL glass vial containing 1000 mg acetaminophen (10 mg/mL). OFIRMEV should be stored at 20 °C to 25 °C (68 °F to 77 °F). Do not refrigerate or freeze.¹
9. CONCLUSION

OFIRMEV is the first and only IV formulation of acetaminophen available in the US, offering an IV analgesic treatment option when an IV route of administration and/or rapid onset of action are desirable. 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. Only OFIRMEV provides the option to use acetaminophen as part of a multimodal IV analgesic regimen.

OFIRMEV offers:

- Significant pain relief\(^3\)
- Reduced opioid consumption\(^2,5\)
- Improved patient satisfaction\(^2,3\)
- Established safety profile and well tolerated in clinical trials\(^1,5\)

IV acetaminophen has been studied in published RCTs across all surgical contexts, from minor outpatient to complicated or major inpatient surgery.\(^2\)

Additionally, OFIRMEV has an established safety profile and was well tolerated in clinical trials. OFIRMEV has no black box warnings, and is not associated with cardiovascular events, gastrointestinal bleeding, respiratory depression, dependency, or platelet dysfunction.

Given its documented efficacy in a wide range of surgeries and well-understood safety profile, OFIRMEV fills an unmet medical need for an effective and well-tolerated nonopioid and non-NSAID analgesic.

**Important Safety Information**

OFIRMEV should be administered only as a 15-minute infusion.

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 is contraindicated in patients with severe hepatic impairment, severe active 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 the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.

Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur.

Do not use in patients with acetaminophen allergy.

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.

The antipyretic effects of OFIRMEV may mask fever in patients treated for postsurgical pain.
ABBREVIATIONS

AE  adverse event
APAP  acetaminophen
AUC  area under the concentration vs time curve
AUC$_\tau$  area under the concentration vs time curve over the dosing interval $\tau$
BMS  Bristol-Myers Squibb
CL  clearance
C$_{\text{max}}$  maximum concentration
CNS  central nervous system
CSF  cerebrospinal fluid
CYP  cytochrome
GI  gastrointestinal
IM  intramuscular
IV  intravenous
LS  least-squares
MAXPAR  maximum pain relief score
MAXPID  maximum pain intensity difference score from baseline
MCID  minimally clinically important difference
NAPQI  $N$-acetyl-$p$-benzoquinone imine
NSAID  nonsteroidal anti-inflammatory drug
PAR  pain relief
PCA  patient-controlled analgesia
PID  pain intensity difference
PK  pharmacokinetics
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA</td>
<td>postmenstrual age</td>
</tr>
<tr>
<td>PO</td>
<td>per os (oral)</td>
</tr>
<tr>
<td>PR</td>
<td>per rectum (rectal)</td>
</tr>
<tr>
<td>Q4h</td>
<td>every 4 hours</td>
</tr>
<tr>
<td>Q6h</td>
<td>every 6 hours</td>
</tr>
<tr>
<td>Q8h</td>
<td>every 8 hours</td>
</tr>
<tr>
<td>Q12h</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>RSE</td>
<td>reference standard endotoxin</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SPID</td>
<td>weighted sum of pain intensity score differences</td>
</tr>
<tr>
<td>T½</td>
<td>elimination half-life</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>Tₘₐₓ</td>
<td>time to reach maximum concentration</td>
</tr>
<tr>
<td>T-MAXPAR</td>
<td>time to maximum pain relief</td>
</tr>
<tr>
<td>T-MAXPID</td>
<td>time to maximum pain intensity difference score from baseline</td>
</tr>
<tr>
<td>TOTPAR</td>
<td>weighted sum of pain relief scores</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analog scale</td>
</tr>
<tr>
<td>Vₜₗ</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>Vₜₗss</td>
<td>volume of distribution at steady state</td>
</tr>
<tr>
<td>WSTD2</td>
<td>weighted sum of the temperature difference to 2 hours</td>
</tr>
<tr>
<td>WSTD6</td>
<td>weighted sum of the temperature difference to 6 hours</td>
</tr>
</tbody>
</table>
REFERENCES

1. OFIRMEV™ (acetaminophen) injection prescribing information. Cadence Pharmaceuticals, Inc.
20. Caldolor® (ibuprofen) injection prescribing information, Cumberland Pharmaceuticals Inc.


