Improved acute pain management starts here

Indication
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.

Important Safety Information
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.

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

Please see full Prescribing Information.
Treatment of acute pain remains suboptimal

Opioids have historically been the foundation for acute pain management²

- In a 2012 research database of 1,665,418 patients, 72% of inpatients treated with IV analgesia received IV opioid monotherapy³

<table>
<thead>
<tr>
<th>72% opioid only</th>
<th>28% other</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1,205,744</td>
<td>n=459,674</td>
</tr>
</tbody>
</table>

- Opioid analgesics rank among the drugs most frequently associated with adverse events³,⁴

Patients continue to report significant post-op pain despite the availability of effective analgesics⁵,⁶

- In a 2012 survey, approximately 85% of patients reported post-op pain, with a total of 65% reporting pain as moderate to extreme⁶

- 80% of patients who received analgesic medications reported adverse events; the most common adverse events reported were drowsiness (56%), constipation (35%), and nausea (28%)⁶
Multimodal analgesia can help optimize pain management with less opioids\textsuperscript{4,7}

Consider a multimodal approach for balanced pain management

- Multimodal analgesia combines 2 or more analgesic agents or techniques that act by different mechanisms to provide analgesia with better pain relief and less opioids\textsuperscript{4,7}

When used in combination with opioids, non-opioid treatments may reduce the dose of opioids required to effectively manage pain\textsuperscript{3}

Use caution when administering acetaminophen in patients with the following conditions:

- Hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min)
Multimodal analgesia is widely supported

The multimodal concept is supported by numerous professional and regulatory organizations

2012 American Society of Anesthesiologists (ASA) Guideline Recommendations for Acute Pain Management— “Whenever possible, anesthesiologists should use multimodal pain management therapy. Unless contraindicated, patients should receive an around the clock regimen of COXIBs, NSAIDs, or acetaminophen.”

2011 American Society for Pain Management Nursing (ASPMN) Guideline Recommendations for Analgesic Pharmacotherapy— “Nurses should act as strong advocates for pain management plans that incorporate opioid dose-sparing strategies initiated early in the course of treatment, eg, on admission, before surgery, during surgery, and early after surgery. Multimodal analgesic therapy that combines opioids with nonopioids, eg, acetaminophen, NSAIDs, anticonvulsants, and antidepressants, has proven efficacy in the treatment of pain.”

2008 Agency for Healthcare Research and Quality (AHRQ) Handbook for Nurses— “The objective for postsurgical and procedural pain is to prevent and control pain...A multimodal approach (balanced analgesia), which includes opioids, nonopioids such as NSAIDs, and adjuvant medications such as anticonvulsants, is recommended...When more than one analgesic is used, the same level of pain relief may be achieved with a lower dose of each analgesic.”

2013 Society of Critical Care Medicine (SCCM) Clinical Practice Guidelines— “We suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether)...For non-neuropathic pain, nonopioids such as IV acetaminophen, oral, IV, or rectal cyclooxygenase inhibitors, or IV ketamine can be used in addition to opioids. Using nonopioids may also decrease the overall quantity of opioids administered and the incidence and severity of opioid-related side effects.”

2012 The Joint Commission (TJC) Sentinel Event Alert— “A multimodal approach combines strategies such as psychosocial support, coordination of care, the promotion of healthful behaviors, nonpharmacologic approaches, and nonopioid pain medications. Upon assessment, the best approach may be to start with a non-narcotic.”
Multimodal analgesia in practice

American Society of Anesthesiologists (ASA) guidelines

- The ASA Task Force recommends the use of multimodal analgesia whenever possible in the perioperative setting.
- Patients should receive an around-the-clock regimen of acetaminophen, NSAIDs, or COX-2 inhibitors unless contraindicated.
- Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events.

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

Step 1: Mild Pain
- Acetaminophen, NSAIDs, or COX-2 selective inhibitors
- Local/regional anesthesia

Step 2: Moderate Pain
- Step 1 and Low doses of opioids

Step 3: Severe Pain
- Step 1 + Step 2 and Higher doses of opioids

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

OFIRMEV is contraindicated in:
- Patients with severe hepatic impairment or severe active liver disease

OFIRMEV (acetaminophen) injection
1000 mg/100 mL (10 mg/mL)
OFIRMEV® (acetaminophen) injection 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. Please see full Prescribing Information.

**In pharmacokinetic studies**

**Rapid onset of action with IV acetaminophen**

OFIRMEV 1 g demonstrated early and high $C_{\text{max}}$ at 15 minutes$^{15,16}$

<table>
<thead>
<tr>
<th>Mean plasma concentrations of OFIRMEV 1 g and oral acetaminophen 1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to reach $C_{\text{max}}$ ($T_{\text{max}}$)</strong></td>
</tr>
<tr>
<td><strong>Mean plasma concentration (μg/mL)</strong></td>
</tr>
<tr>
<td>OFIRMEV 1 g (N=38)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
</tr>
<tr>
<td>0.75</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

- $C_{\text{max}}$ occurs at the end of the 15-minute IV infusion of OFIRMEV$^{16}$
- Overall exposure (AUC) after a single dose was similar to oral acetaminophen$^{15,16}$
- No significant accumulation with repeated dosing$^{15,16}$

**Begin your IV analgesic regimen with OFIRMEV**

- Rapid onset of action$^{16}$
- Early and high $C_{\text{max}}$ $^{16}$
- No first-pass hepatic exposure$^{16}$
- 100% bioavailability$^{16}$

**Do not exceed the maximum recommended daily dose of 4 g of acetaminophen by all routes**

OFIRMEV® (acetaminophen) injection 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. Please see full Prescribing Information.
**In pharmacokinetic studies**

**Greater peak levels with IV acetaminophen**

OFIRMEV 1 g was associated with greater peak plasma levels\(^1\)\(^7\)

<table>
<thead>
<tr>
<th>Mean plasma concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time (h)</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>2.5</td>
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<td>5.1</td>
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<tr>
<td>7.5</td>
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<tr>
<td>10</td>
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<td>15</td>
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<td>17.5</td>
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<td>20</td>
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<tr>
<td>22.5</td>
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<tr>
<td>25</td>
</tr>
<tr>
<td>27.5</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

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

- Peak plasma concentrations were 76% higher than oral acetaminophen \((P=0.0004)\) and 256% higher than rectal acetaminophen \((P<0.0001)\)\(^7\)
- Efficacy was not assessed in this study

**OFIRMEV 1 g was associated with greater cerebrospinal fluid (CSF) levels\(^1\)\(^7\)**

<table>
<thead>
<tr>
<th>Mean CSF concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time (h)</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
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<tr>
<td>1</td>
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<tr>
<td>1.5</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
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<td>4.5</td>
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<tr>
<td>5</td>
</tr>
<tr>
<td>5.5</td>
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<td>6</td>
</tr>
</tbody>
</table>

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

- Peak CSF concentrations were 60% higher than oral acetaminophen \((P<0.0001)\) and 87% higher than rectal acetaminophen \((P<0.0001)\). No significant difference was seen between oral and rectal groups.\(^7\)
- Efficacy was not assessed in this study
“Altered gastric emptying may result in changes in the rate of absorption of orally administered drugs...”

Several factors may diminish gastric function following surgery:

- Significant delays in gastric emptying occur with the administration of IV opioid analgesics.
- Absorption of oral acetaminophen is diminished due to compromised gastric function.
Effect of opioids on gastric emptying and oral absorption in surgical patients

Opiate-related pyloric narrowing or closure led to decreased concentration levels of oral acetaminophen\textsuperscript{19}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Peak plasma levels of oral acetaminophen on Day 1}
\end{figure}

- Oral acetaminophen absorption was decreased following nasogastric administration due to opioid use\textsuperscript{19}

Morphine markedly delayed the absorption of oral acetaminophen\textsuperscript{18}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Mean pre-op and post-op plasma concentrations}
\end{figure}

- Post-op plasma concentrations of oral acetaminophen (when used as a marker for gastric absorption) were significantly lower than pre-op values ($P<0.001$) in patients who received opioids following surgery\textsuperscript{18}
- Post-op $C_{\text{max}}$ and $T_{\text{max}}$ of oral acetaminophen could not be determined following morphine administration due to a marked delay in absorption\textsuperscript{18}

Berger et al Prospective pharmacokinetic study conducted in patients who underwent cardiac surgery (n=16) and healthy volunteers who served as controls (n=6) to assess intestinal absorption as a function of placement of tube insertion. As a marker to assess absorption, 1 g of acetaminophen in liquid formulation was administered on post-op days 1 and 3 through a nasogastric (n=11) or postpyloric tube (n=5).

Petring et al Randomized, double-blind, pharmacokinetic study involving 15 patients undergoing orthopaedic surgery with spinal anaesthesia. Upon first complaint of post-op pain, patients were randomized to receive a single dose of intramuscular morphine 10 mg (n=8) or a single dose of intramuscular ketorolac 30 mg (n=7). Oral acetaminophen solution 20 mg/kg was administered twice in each patient as a marker, at least 12 h before scheduled surgery (pre-op) and 30 minutes after administration of morphine (post-op).
In orthopaedic surgery

**Significant pain relief**

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

![Graph showing pain relief](image)

Significantly reduced pain intensity over 24 h²²

- OFIRMEV showed a greater reduction in pain intensity over 24 h (SPID24)¹ compared to placebo ($P<0.001$)²²

**OFIRMEV is contraindicated in:**

- Patients with severe hepatic impairment or severe active liver disease

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In orthopaedic surgery

Reduced opioid consumption

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

![](chart.png)

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

Significant improvement in (median) time to first rescue medication

- 3 h vs 0.8 h for OFIRMEV 1 g vs placebo ($P<0.0001$)

Patient satisfaction with study treatment was also significantly higher for OFIRMEV 1 g vs placebo

- 40.8% vs 23.1% of patients reporting good or excellent satisfaction over PCA morphine alone ($P=0.004$)
- Patients were asked to evaluate the study treatments overall, using a 4-point categorical scale

Most common adverse reactions in adult patients

- Nausea, vomiting, headache, insomnia

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.
**In acute renal colic**

**Rapid reduction of pain intensity**

**IV acetaminophen 1 g reduced pain intensity at 15 and 30 minutes in the emergency department setting**

<table>
<thead>
<tr>
<th>Pain intensity scores, single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median pain intensity (VAS 100 mm)</strong></td>
</tr>
<tr>
<td><strong>0</strong></td>
</tr>
<tr>
<td><strong>20</strong></td>
</tr>
<tr>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

**Significant reductions in pain intensity vs placebo for IV acetaminophen 1 g and IV morphine**

- Significant mean differences in pain intensity reductions were observed for IV acetaminophen ($P=0.005$) and IV morphine ($P=0.045$) when compared with placebo.
- This study was not designed as a head-to-head, noninferiority trial.

**Do not exceed the maximum recommended daily dose of 4 g of acetaminophen by all routes.**

**In acute renal colic**

**Rapid reduction of pain intensity**

**IV acetaminophen 1 g reduced pain intensity at 15 and 30 minutes in the emergency department setting**

**Bektas et al.** Randomized, prospective, double-blind, placebo-controlled, single-center, single-dose trial with 3 parallel groups. Patients received a single dose of IV acetaminophen 1 g, IV morphine 0.1 mg/kg, or placebo upon presenting to the emergency department with suspected renal colic. IV fentanyl was available to patients with inadequate pain relief at 30 minutes. Primary endpoint: change in pain intensity, based on VAS score, from baseline, at 15 and 30 minutes.

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In acute renal colic

Use of rescue analgesia

Fewer patients receiving IV acetaminophen 1 g vs placebo required rescue analgesia following 30-minute study period

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>OFIRMEV 1 g (n=46)</th>
<th>IV morphine 0.1 mg/kg (n=49)</th>
<th>Placebo (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46%</td>
<td></td>
<td>49%</td>
<td>68%</td>
</tr>
</tbody>
</table>

\[P=NS \text{ vs placebo}\]

Bektaş et al. Randomized, prospective, double-blind, placebo-controlled, single-center, single-dose trial with 3 parallel groups. Patients received a single dose of IV acetaminophen 1 g, IV morphine 0.1 mg/kg, or placebo upon presenting to the emergency department with suspected renal colic. IV fentanyl was available to patients with inadequate pain relief at 30 minutes. Primary endpoint: change in pain intensity, based on VAS score, from baseline, at 15 and 30 minutes.

- Rescue analgesics at 30 minutes were required by 46% of patients receiving IV acetaminophen, 49% of patients receiving IV morphine, and 68% of patients receiving placebo \((P=NS)\)
- The clinical benefit of reduced opioid consumption was not evaluated or demonstrated

Most common adverse reactions in adult patients
- Nausea, vomiting, headache, insomnia
OFIRMEV® (acetaminophen) injection 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. Please see full Prescribing Information.

In abdominal laparoscopy

Reductions in pain intensity

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

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

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

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

Improved patient satisfaction

Patients’ evaluations of study treatments were significantly higher for OFIRMEV 1 g vs placebo24

**Patient-reported satisfaction with study treatment at 24 h**

<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>

*P=0.0004*

• Patients were asked to evaluate the study treatments overall, using a 4-point categorical scale

Study encompassed laparoscopic OB/GYN and general surgical procedures24:

• Hysterectomy
• Cholecystectomy
• Hernia repair
• Prostatectomy

Use caution when administering acetaminophen in patients with the following conditions:

• Hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min)

*Overall P value derived from a statistical analysis of a 4-point categorical scale.

Wininger et al (Pain Study 2)
Randomized, double-blind, placebo-controlled, multicenter, parallel-group study. The morning following abdominal laparoscopic surgery, patients received OFIRMEV 1 g or placebo q6h or OFIRMEV 650 mg or placebo q4h. IV or oral rescue medication was available to all patients. Primary endpoint: SPI24 (sum of pain intensity differences, based on VAS score, from baseline, at 0 to 24 h).
**In abdominal hysterectomy**

**Administer IV acetaminophen pre-op to improve post-op pain control**

Pre-op administration of IV acetaminophen 1 g demonstrated greater reductions in pain intensity vs placebo over 24 h\(^25\)

<table>
<thead>
<tr>
<th>Mean pain intensity scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Value</td>
</tr>
<tr>
<td>4.0</td>
</tr>
<tr>
<td>3.5</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>2.5</td>
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<tr>
<td>2.0</td>
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<td>1.5</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
</tbody>
</table>

- *Post-op pain intensity scores were significantly lower at all time points for the IV acetaminophen groups (pre-op and intra-op) compared to placebo (\(P<0.05\))\(^25\)

**Use caution when administering acetaminophen in patients with the following conditions:**

- Hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min)

**Do not exceed the maximum recommended daily dose of 4 g of acetaminophen by all routes**

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OFIRMEV\(^\text{®}\) (acetaminophen) injection 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. Please see full Prescribing Information.
In abdominal hysterectomy

Administer IV acetaminophen pre-op to significantly reduce opioid use

Pre-op administration of IV acetaminophen 1 g resulted in significantly less total opioid consumption over 24 h²⁵

![Morphine consumption over 24 h](image)

- Post-op morphine consumption was significantly lower among the IV acetaminophen groups (pre-op and intra-op) compared to placebo (P<0.05)²⁵
- When administered pre-op, IV acetaminophen 1 g demonstrated a significantly greater reduction in morphine consumption compared to the same dose administered intra-op (P<0.05)²⁵
- The clinical benefit of reduced opioid consumption was not evaluated or demonstrated

OFIRMEV is contraindicated in:

- Patients with severe hepatic impairment or severe active liver disease
OFIRMEV—established safety profile and well tolerated in clinical trials

Most common adverse reactions
- Adult patients: nausea, vomiting, headache, and insomnia
- Pediatric patients: nausea, vomiting, constipation, pruritus, agitation, and atelectasis

OFIRMEV was not associated with the following side effects in clinical trials:
- Respiratory depression, postoperative ileus, sedation, cognitive impairment in older patients, upper gastrointestinal bleeding, surgical site bleeding, renal toxicity, platelet inhibition, or cardiovascular thrombotic events

Liver enzyme elevations were comparable to placebo

| Peak ALT/AST values postbaseline: % of patients in all repeated-dose, placebo-controlled, all-adult studies |
|-------------------------------------------------|-------------------|-------------------|
|                                                 | IV acetaminophen (n=402) | Placebo (n=379) |
| ALT >3× ULN                                     | 1.1% (n=4)           | 1.7% (n=6)        |
| ALT >5× ULN                                     | 0.3% (n=1)           | 0.6% (n=2)        |
| AST >3× ULN                                     | 1.0% (n=4)           | 1.1% (n=4)        |
| AST >5× ULN                                     | 0.5% (n=2)           | 0.8% (n=3)        |

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

OFIRMEV 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 approved for use in patients ≥2 years of age

OFIRMEV is contraindicated in:
• Patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation
• Patients with severe hepatic impairment or severe active liver disease

Warnings and precautions
• Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death
• Do not exceed the maximum recommended daily dose of acetaminophen
• Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min)
• Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy.

Drug interactions
• Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential
• 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
Recommended dosing of OFIRMEV

<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)</td>
<td>q6h</td>
<td>1000 mg (100 mL)*</td>
<td>4000 mg in 24 hours</td>
</tr>
<tr>
<td>Adults and adolescents (≥13 years old)</td>
<td>q6h</td>
<td>Weight-based dose: 15 mg/kg (up to 750 mg)</td>
<td>75 mg/kg in 24 hours (up to 3750 mg)</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.

- Minimum dosing interval is q4h.
- For instructions regarding q4h dosing, please see full Prescribing Information.
- No dose adjustment is required when transitioning to oral acetaminophen in adults and adolescents.
- OFIRMEV should be administered only as a 15-minute infusion. Administer only as directed.

Use caution when administering acetaminophen in patients with the following conditions:
- Hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤30 mL/min)
OFIRMEV from the start

Administer OFIRMEV pre-op, then schedule q6h

CONTINUE WITH OFIRMEV IF:
- Parenteral analgesia is clinically warranted
- Compromised GI absorption or inability to take oral analgesics
- 100% bioavailability desired

TRANSITION TO ORAL ANALGESIA WHEN:
- Patient can take and absorb oral analgesics

Do not exceed the maximum recommended daily dose of 4 g of acetaminophen by all routes
- Administration of acetaminophen by any route in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death

References:
Less pain. Less opioids. From the start.

Begin your multimodal analgesic regimen with OFIRMEV®

- Significant pain relief
- Reduced opioid consumption
- Improved patient satisfaction
- Established safety profile and well tolerated in clinical trials
- Utilization considerations:
  - Initiate early (pre-op or intra-op)
  - Schedule q6h for the first 24 h or as long as clinically warranted
  - Do not exceed the maximum recommended daily dose of 4 g of acetaminophen by all routes

Indication

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.

Important Safety Information

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.

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-minute infusion.

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.

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Cadence Pharmaceuticals, Inc. at 1-877-647-2239 or FDA at 1-800-FDA-1088 or http://www.fda.gov/Safety/MedWatch/default.htm.

Please see accompanying full Prescribing Information.
FULL PRESCRIBING INFORMATION
INDICATIONS AND USAGE
OFIRMEV® (acetaminophen) injection is indicated for:
The management of moderate to mild pain with
adjunctive analgesics
The use caution when administering acetaminophen in patients
with the following conditions: hepatic impairment or active
hepatitis, in doses of more than 10 g/day; chronic malnutrition,
severe hypovolemia, or severe renal disease;
Discontinue OFIRMEV immediately if symptoms suggestive of
hepatotoxicity occur. Do not use in patients with acetaminophen
allergy. (5.2)

ADVERSE REACTIONS
The most common adverse reactions in patients treated with
OFIRMEV were nausea, vomiting, headache, and insomnia
in adult patients and nausea, vomiting, somnolence, agitation,
and anorexia in pediatric patients. (6.1)

Dosage and Administration
OFIRMEV may be given as a single or repeated dose. (2.1)

OFIRMEV should be administered only as a 15-minute
intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:
1000 mg every 6 hours or 650 mg every 4 hours to a
maximum of 75 mg/kg per day. Minimum dosing interval
of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:
15 mg/kg every 6 to 12.5 mg/kg every 4 hours to a
maximum of 75 mg/kg per day. Minimum dosing interval
of 4 hours. (2.2)

DOSAGE FORMS AND STRENGTHS
OFIRMEV is available in a single vial containing:

Each 195 mg vial contains 1000 mg acetaminophen
(20 mg/mL) as an acetate. (3.1)

CONTRAINDICATIONS
Acetaminophen is contraindicated in:
any of the conditions described above;

WARNINGS AND PRECAUTIONS

Adolescents weighing more than 75 kg:
Adolescents weighing more than 75 kg should receive:

Adolescents weighing 75 kg and over:

Upon the completion of the infusion in order to alert healthcare practitioners that the antipyretic
and/or analgesic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies
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=171) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 1.1% (n=11) and 1.0% (n=10) of patients treated with OFIRMEV doses up to 15 mg/kg on an every 4 hours schedule and more than 15 mg/kg on an every 4 hours schedule, respectively, reported allergy and hypersensitivity. Do not use OFIRMEV in patients with acetaminophen allergy.

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

Hepatic Injury [see WARNINGS AND PRECAUTIONS (5.1)]]

Allergic reaction [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

5.1 Hepatic Injury
Administration of acetaminophen in doses greater than
recommended may result in hepatic injury, including the
case of severe hepatic necrosis and death. (5.1)

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, angina, rash, and pruritus. There were no recent reports of fatalities requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

7.1 Effects of other Substances on Acetaminophen
Substances that induce or regulate hepatic cytochrome
enzymes CYP2E1 may alter the metabolism of
acetaminophen. (5.1)

The safety and effectiveness of OFIRMEV in pediatric patients
less than 2 years of age is supported by evidence from adequate and
well-controlled studies. (8.5)

The safety and effectiveness of OFIRMEV in pregnant women. Use only if clearly
needed. (7.2)

8.8 Pregnancy
OFIRMEV contains acetaminophen, a pregnancy
Category B drug. (8.1)

Clinical Trials of OFIRMEV in Pediatrics
The following additional treatment-emergent adverse reactions were reported by pediatric
subjects treated with OFIRMEV (n=355) that were not also reported by adult subjects:

Blood and lymphatic system disorders:
anemia
Cutaneous disorders: tachycardia
Digestive disorders: pruritus
Endocrine disorders: pruritus
Lymphatic disorders: pruritus
Skin disorders: gingival hyperplasia
Subcutaneous disorders: pain
Vascular disorders: hypertension

Pediatric population
A total of 335 pediatric patients (47 neonates, 64 infants, 171 children, and 14 adolescents)
with age range from birth to 18 years have received OFIRMEV in active-controlled 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 receiving OFIRMEV doses up to 15 mg/kg on an every 4 hours schedule and more than 15 mg/kg on an every 4 hours schedule, respectively, reported allergy and hypersensitivity. 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.

General disorders and administration site:
Injection site pain, edema periorbital, pyrexia
Hepatic enzyme increase
Metabolism and nutrition disorders:
yellowish discoloration, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia
Musculoskeletal and connective tissue disorders:
muscle spasm, pain in extremity
Nervous system disorders:
Psychiatric disorders:
Insomnia
Reproductive, thoracic and mediastinal disorders:
pulmonary edema, hypoxia, pleural effusion, pleural thickening
Skin and subcutaneous tissue disorders:
pruritus, edema periorbital, rash
Vascular disorders:
hypertension, hypotension

7.2 Anticoagulants
Acetaminophen, when administered in high doses,
can decrease the anticoagulant effect of warfarin.

9.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

12.2 Pharmacodynamics
The effectiveness of OFIRMEV was demonstrated in a
comparing converting between oral acetaminophen and
acetaminophen. (8.7)

12.5 Pharmacokinetics
OFIRMEV is not intended for use in patients weighing
less than 75 kg. OFIRMEV is a single-use vial and the

Table 1: Dosing for Adults and Adolescents

<table>
<thead>
<tr>
<th>Age group</th>
<th>Recommend dosage of OFIRMEV</th>
<th>Dosing interval</th>
<th>Maximum daily dose of acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 year old</td>
<td>15 mg/kg or 500 mg daily</td>
<td>4 hours</td>
<td>75 mg/kg in 24 hours</td>
</tr>
<tr>
<td>1-12 years old</td>
<td>15 mg/kg or 1250 mg daily</td>
<td>4 hours</td>
<td>75 mg/kg in 24 hours</td>
</tr>
<tr>
<td>≥13 years old</td>
<td>15 mg/kg or 1000 mg daily</td>
<td>4 hours</td>
<td>75 mg/kg in 24 hours</td>
</tr>
</tbody>
</table>

9.2 Long-Term Studies

12.2 Pharmacodynamics
The effectiveness of OFIRMEV was demonstrated in a
comparing converting between oral acetaminophen and
acetaminophen. (8.7)

12.5 Pharmacokinetics
OFIRMEV is not intended for use in patients weighing
less than 75 kg. OFIRMEV is a single-use vial and the
in international normalized ratio (INR) in some patients who have been stabilized on warfarin as an anticoagulant. As no studies have been performed with the total dose of OFIRMEV in patients on oral anticoagulants, more frequent monitoring 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. Acetaminophen is known to cross the placenta and reach the fetal circulation. There is no evidence of harm when administered to a pregnant woman. OFIRMEV is not given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort study, including data from 26,242 women with live singletons who were exposed to oral acetaminophen during the first trimester of pregnancy, and from multiple birth and other birth outcomes, compared to a control group of unexposed children. The rate of congenital anomalies (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study examined the risk of oral acetaminophen in pregnant women with prepregnancy obesity and with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to a 4,500 patient control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, the results of reproduction and fertility studies show that receipt of acetaminophen during organogenesis at doses up to 8.8 mg/kg/day (2.5 mg/kg/day, the 32 weeks post-conception 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 (2.5)].

8.2 Pediatric Use

The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients < 2 years of age is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 335 patients across the full pediatric age strata, from healthy children to children with chronic conditions and to adolescents. The effectiveness of acetaminophen intended for intravenous infusion. The pharmacokinetics and clinical effects of acetaminophen were studied in Swiss mice via a continuous dosing protocol. In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the mouse bone marrow micronucleus test. In the mouse bone marrow micronucleus test, there was no evidence of carcinogenic activity in male rats (0.7 times) or female rats (0.7 times) in the in vitro mouse lymphoma assay and the mouse bone marrow micronucleus test. The following table provides a summary of the pharmacokinetic and clinical effects of acetaminophen in mice consuming the calculated infant daily dose of acetaminophen. 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 2-year-old patient after treatment of acute ingestion. The acetaminophen level was 7.5 mg/mL at 12 hours. If serum level is above the lower limit, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower limit. For additional information, call a poison control center at 1-800-222-1222.

11 DESCRIPTION

Acetaminophen is non-salicylate antipyretic and non-opioid analgesic agent. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular formula C8H9NO2. It is a white, odorless, crystalline substance. It is soluble in water (40 mg/mL at room temperature) and freely soluble in alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not clearly established but is thought to primarily involve central actions.

12.2 Absorption

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human models.

10 OVERDOSAGE

10.1 S Ramos and Symptoms

In acute overdose situations, acetaminophen is considered a weak hepatotoxin. Acetaminophen overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent for 38 to 72 hours post-ingestion.

12.3 Pharmacokinetics

The pharmacokinetic and clinical effects of acetaminophen were studied in Swiss mice via a continuous dosing protocol. 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 minus half-life interval of 6 hours, will produce a pharmacokinetic exposure equivalent 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.

14 CLINICAL STUDIES

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain is established in one randomized, double-blind, placebo-controlled clinical trial in adults with postoperative pain.

14.2 Adult Fever

OFIRMEV was studied in 355 pediatric patients across the full pediatric age strata, from healthy children to children with chronic conditions and to adolescents. The effectiveness of acetaminophen intended for intravenous infusion. Of 1277 patients, 96 patients had an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m2. As a guide to treatment of acute ingestion. Obtain liver function studies initially as possible. As a guide to treatment of acute ingestion. Obtain liver function studies initially as possible. As a guide to treatment of acute ingestion. Obtain liver function studies initially as possible. As a guide to treatment of acute ingestion. Obtain liver function studies initially as possible.