The Role of Multimodal Analgesia In General Surgery

A Review of Clinical Data and Case-Based Presentations Featuring OFIRMEV® (acetaminophen) Injection

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INDICATIONS AND USAGE

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

IMPORTANT RISK INFORMATION

WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY
Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:
- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product.

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

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Introduction

Effective pain management is a nationwide priority for health care organizations, practitioners, and policymakers. Over the past 2 decades, the suboptimal treatment of acute pain has become an important issue in health care, specifically in the postoperative setting. For example, The Joint Commission instituted pain management standards for the assessment and management of acute pain in 2001. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, also known as the CAHPS, is the first national, standardized, publicly reported survey of patients' perspectives on hospital care. Included in the HCAHPS survey are questions regarding pain management. The scores are available to the public and allow patients to compare hospitals in a meaningful manner.

Patient satisfaction is an increasingly important outcome when considering perioperative analgesic regimens.

Unmet Need in Pain Management

Despite the increased focus on pain management and the availability of effective analgesics and new mechanisms for delivering pain medications in the immediate postoperative period over the past 2 decades, the incidence of postoperative pain remains high. In a 2012 survey, approximately 85% of patients reported postoperative pain; of those, 65% reported moderate to extreme pain. These data are similar to those from a survey conducted in 1995 (65% vs. 63% of patients reported moderate to extreme postoperative pain, respectively).

Postoperative pain is associated with various complications and poor outcomes. Postoperative pain also is one of the most common reasons for hospital readmission following discharge.

Traditionally as well as currently in the US, monotherapy with opioids is used as the mainstay to treat postoperative pain. In a 2012 study analyzing data from 1,665,418 hospital patients, 72% of inpatients treated with IV pain medication received IV narcotic monotherapy.

These factors make pain management challenging in postoperative patients. In 2012, The Joint Commission published a Sentinel Event Alert that underscored the need for judicious and safe use of opioids in hospitals. Included in The Joint Commission’s recommendations were measures aimed at reducing the overall use of opioids, such as implementing a multimodal approach to perioperative analgesia.

Multimodal Approach to Pain Management

Acute postoperative pain is complex and multifactorial and may be optimally treated via a multimodal approach in the perioperative setting. With this approach, 2 or more analgesics acting by different mechanisms are administered when providing analgesia. Using different classes of analgesics, each with different pathways and receptors, multimodal analgesia can optimize analgesic efficacy by using lower doses of each of the respective agents, with the aim to reduce the risk for dose-related adverse effects (AEs).

Multimodal analgesia may be implemented via a stepwise approach with nonopioids serving as the foundational agents given perioperatively for the management of pain with adjunctive opioids added as needed for moderate to severe pain.

Over the past decade, multimodal analgesia has gained recognition as an effective strategy for the management of acute pain in the perioperative setting, and the concept is supported by numerous professional organizations. The American Society of Anesthesiologists (ASA), the American Society for Pain Management Nursing (ASPMN), the Agency for Healthcare Research and Quality (AHRQ), and The Joint Commission encourage a multimodal approach to perioperative analgesia. Current ASA guidelines recommend that unless contraindicated, all surgical patients should receive an around-the-clock regimen of a nonopioid agent, such as acetaminophen, nonsteroidal anti-inflammatory drug (NSAID), or cyclooxygenase-2 selective NSAID (COXIB).

OFIRMEV® (acetaminophen) Injection

Product Description

Acetaminophen is a non-salicylate, non-NSAID, nonopioid analgesic and antipyretic agent. The precise mechanism(s) of the analgesic and antipyretic properties of acetaminophen is not established, but is thought to primarily involve central actions.

OFIRMEV is the first and only IV formulation of acetaminophen available in the United States. OFIRMEV is indicated for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever. OFIRMEV is approved for use in patients at least 2 years of age.

Clinical Pharmacology of OFIRMEV

The pharmacokinetics and pharmacodynamics of IV acetaminophen have been well characterized (Figures 1 and 2).
In a pharmacokinetic study conducted by Cadence Pharmaceutical Inc., IV acetaminophen was compared with oral acetaminophen.\textsuperscript{13} Compared with a 1-g dose of oral acetaminophen, 1 g of IV acetaminophen shows up to 70% higher maximum plasma concentration (C\text{max}), with a median time to reach C\text{max} (T\text{max}) at 15 minutes (end of infusion). Area under the concentration-time curve (AUC) is very similar for the same dose of IV acetaminophen and oral acetaminophen.\textsuperscript{13} The peak effect of 1 g acetaminophen occurs within 1 hour of administration and duration of effect is 4 to 6 hours.\textsuperscript{15} Additionally, there is no evidence of clinically significant drug accumulation with repeated dosing.\textsuperscript{16}

In a second pharmacokinetic study by Singla and colleagues, the plasma and cerebrospinal fluid (CSF) pharmacokinetics of IV, oral, and rectal acetaminophen were compared. Six healthy male patients were included in a 3-way, crossover, single-center, single-dose design pharmacokinetic study. The IV route produced a 76% higher mean plasma C\text{max} (P=0.0004) than oral and a 256% higher C\text{max} (P<0.0001) than rectal administration of acetaminophen (Figure 1). The T\text{max} for the IV route was earlier (0.25 h) than that for the oral route (1 h, P=0.0018) or the rectal route (2.5 h, P=0.0025).\textsuperscript{14}

In this study, the mean CSF AUC for IV acetaminophen over 6 hours was 75% higher than the oral AUC (P=0.0099) and 142% higher than the rectal AUC (P=0.0004). The mean CSF C\text{max} value for IV acetaminophen was 59.7% higher than that for oral (P<0.0001) and 86.8% higher than that for rectal administration (P<0.0001; Figure 2).\textsuperscript{14}

**Clinical Considerations Regarding Route Of Administration**

Surgery, opioids, anesthesia, preoperative fasting, and postoperative stress can all work together in the period immediately following surgery to produce gastroparesis and delayed gastric emptying (Figure 3). These factors are important when choosing the appropriate formulation of acetaminophen in the perioperative setting as absorption of oral analgesics may be compromised in the immediate postoperative setting.\textsuperscript{17-20}

Following surgery, compromised gastric function has been shown to diminish the absorption of oral acetaminophen. In a prospective pharmacokinetic study designed to assess absorption, Berger and colleagues demonstrated that opiate-related pyloric narrowing or closure leads to decreased plasma concentrations of acetaminophen given orally.\textsuperscript{18}

Additionally, a study by Petring and colleagues confirmed that significant delays in gastric emptying occur with the administration of IV opioid analgesics. When used as a gastric absorption marker, postoperative plasma concentrations after acetaminophen given orally were significantly lower than preoperative values (P<0.001) in patients who received opioids after surgery.\textsuperscript{17}

**Analgesic Efficacy of OFIRMEV**

As part of an extensive clinical data set consisting of numerous randomized controlled trials (RCTs), IV acetaminophen has demonstrated a significant analgesic benefit relating to pain relief or reduction in pain intensity, and has

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**Figure 2.** Mean (SD) CSF acetaminophen concentration-time curves after IV, PO, and PR administration of 1,000 mg.
Pharmacokinetic study. Efficacy was not assessed.
AUC, area under the curve; CSF, cerebrospinal fluid; PO, oral; PR, rectal; SD, standard deviation
Based on reference 14.

**Figure 3.** Absorption of oral analgesics may be compromised in the perioperative setting.
Based on references 17-20.
demonstrated analgesic efficacy in a variety of surgery types. Two pivotal studies evaluated OFIRMEV in the treatment of acute postoperative pain after abdominal laparoscopic surgery (soft tissue pain) and major orthopedic surgery (bone and joint pain).

In abdominal laparoscopic surgery, Wininger and colleagues evaluated the analgesic efficacy of repeated doses of IV acetaminophen 1 g or IV placebo 100 mL at 6-hour intervals, or IV acetaminophen 650 mg or IV placebo 65 mL at 4-hour intervals, over 24 hours in 244 patients with moderate to severe postoperative pain following elective laparoscopic surgery (including cholecystectomy, hysterectomy, hernia repair, colonic resection, and prostatectomy). IV or oral opioid rescue medication was available to all patients. Efficacy was measured as the weighted sum of pain intensity differences over 24 hours (SPID24) based on 100-mm visual analog scale (VAS) for the IV acetaminophen 1 g versus combined placebo groups (primary end point); SPID24 based on VAS for the IV acetaminophen 650 mg versus combined placebo groups; pain relief; patients’ global evaluation of study treatment at 24 hours; time to first use of rescue medication; and total amount of rescue medication consumption over 24 hours.21

A significant reduction in SPID24 from baseline was seen with IV acetaminophen 1 g plus rescue when compared with placebo plus rescue (P<0.007; Figure 4). Time to meaningful pain relief after the first dose was significantly shorter in patients who received IV acetaminophen 1 g plus rescue

![Figure 4. Sum of pain intensity differences over 24 hours after abdominal laparoscopic surgery.]

SPID24, sum of pain intensity differences over 24 hours; VAS, visual analog scale

Based on reference 21.

![Figure 5. Mean pain intensity scores at 6-hour intervals after abdominal laparoscopic surgery.]

VAS, visual analog scale; NS, not significant

Based on references 16 and 21.
compared to the matched placebo plus rescue group, with median values of 24.9 versus 53.9 minutes, respectively (P<0.003). Furthermore, an expanded analysis of these study data over 24 hours demonstrated that the mean pain intensity scores were significantly lower for the IV acetaminophen plus rescue group at each dosing interval through 18 hours (Figure 5). In major orthopedic surgery, Sinatra and colleagues evaluated the analgesic efficacy of repeated doses of IV acetaminophen 1 g versus placebo every 6 hours for 24 hours in 101 patients reporting moderate to severe pain following total hip or total knee replacement. Rescue IV patient-controlled analgesia (PCA) morphine was available to all patients. Patients were started on study medication the morning of the first postoperative day to allow for anesthesia washout and to establish a baseline. Efficacy was measured as pain relief on a 5-point verbal scale over 6 hours (primary end point); pain intensity on a 100-mm VAS and a 4-point verbal scale over 24 hours; quantity of morphine consumed; time to first use of rescue medication; and patient satisfaction with pain management at 24 hours.

In the 6-hour, single-dose evaluation period, IV acetaminophen 1 g plus PCA morphine demonstrated superior pain relief versus placebo plus PCA morphine from 15 minutes to 6 hours (Figure 6). In the repeated-dose evaluation period, SPID24 was significantly reduced in the IV acetaminophen group compared with the placebo group (P<0.01).

There were no significant differences between IV acetaminophen and placebo groups regarding the incidence of AEs. Constipation, nausea, anemia, pruritus, and vomiting were the most frequently reported AEs in both groups.

In major abdominal and pelvic surgery in patients requiring a planned admission to the intensive care unit (ICU), Memis and colleagues studied the efficacy of repeated doses of IV acetaminophen 1 g plus IV meperidine versus placebo plus IV meperidine. Patients were assessed for pain using both a behavioral pain scale (BPS) and a VAS. When BPS or VAS values were more than 4, IV meperidine 1 mg/kg was administered. Use of IV acetaminophen plus IV meperidine was associated with significantly lower pain scores as measured by BPS and VAS over 24 hours (Figure 7).

IV acetaminophen also has demonstrated rapid analgesic efficacy versus placebo in an emergency department (ED) setting. In patients presenting to the ED with renal colic, Bektas and colleagues found rapid reductions in pain intensity at 15 and 30 minutes after receiving 1 g of IV acetaminophen versus placebo. IV fentanyl was available to patients with inadequate pain relief at 30 minutes. Statistically significant mean differences in pain intensity reductions compared with those for placebo were observed for IV acetaminophen (odds ratio, 16; 95% confidence interval, 5-27; P=0.005).

Preemptive Analgesic Efficacy of OFIRMEV

As part of a multimodal analgesic approach, the ASA guidelines recommend that preoperative initiation of analgesia for postoperative pain should be considered during patient preparation for perioperative pain management. The following study evaluated the effect of IV acetaminophen on postoperative pain when used preemptively (preoperatively or intraoperatively).
In a study of 90 patients undergoing total abdominal hysterectomy, Arici and colleagues evaluated the effect of IV acetaminophen 1 g given preoperatively (30 minutes before induction), IV acetaminophen 1 g given intraoperatively (at skin closure), or placebo. All patients had PCA morphine freely available as rescue. Results showed that postoperative pain intensity scores were significantly lower for both IV acetaminophen groups, preoperatively and intraoperatively, compared with placebo ($P<0.05$; Figure 8).\(^\text{25}\)

**Reduced Opioid Consumption With OFIRMEV**

Reduced opioid consumption with IV acetaminophen has been demonstrated in a number of RCTs across a variety of surgical procedures with significant reductions compared with placebo (Figures 9-11).\(^\text{15,23,25}\) In total hip and knee replacement, 1 g IV acetaminophen plus PCA morphine significantly reduced morphine consumption compared with placebo plus PCA morphine (–46% over 6 h, $P<0.01$; –33% over 24 h, $P<0.01$; Figure 9). Median time to first rescue medication use was significantly longer with IV acetaminophen compared with placebo (3 h vs 0.8 h, $P=0.0001$).\(^\text{15}\) In major abdominal surgery, postoperative rescue meperidine consumption was reduced by 61% over 24 hours among patients receiving IV acetaminophen compared to placebo (Figure 10).\(^\text{23}\)

Arici and colleagues found that IV acetaminophen plus standard of care demonstrated significantly less morphine consumption over 24 hours when compared to placebo plus standard of care ($P<0.05$; Figure 11). The data in this study suggest that when administered preoperatively, IV acetaminophen 1 g demonstrated a significantly greater reduction in morphine consumption compared to the same dose administered intraoperatively ($P<0.05$).\(^\text{23}\)

Although IV acetaminophen has demonstrated the ability to reduce opioid consumption, the clinical significance of this has not been evaluated or demonstrated.

**Improved Patient Satisfaction With OFIRMEV**

Patient reports of satisfaction with pain management favor IV acetaminophen plus standard of care over placebo plus standard of care in a number of clinical trials and surgery types.

In the study by Wininger and colleagues, patients’ global evaluation of satisfaction with study treatment and satisfaction with AEs related to study treatment were reported at 24 hours. These results significantly favored IV acetaminophen plus rescue over the combined placebo plus rescue (all comparisons, $P<0.001$).\(^\text{21}\) Similar results were demonstrated in the study by Sinatra and colleagues; patients’ global evaluations of study treatment at 24 hours (repeated doses) were significantly more favorable among patients who received IV acetaminophen plus PCA morphine versus patients who received placebo plus PCA morphine. On a 4-point categorical scale, satisfaction scores of good to excellent were significantly greater for IV acetaminophen plus PCA morphine (4.2 vs 3.7; $P<0.05$) compared with placebo plus PCA morphine (4.2 vs 3.7; $P<0.05$).

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**Figure 8.** Mean pain intensity scores following total hysterectomy surgery.

**VAS**, visual analog scale

Based on reference 25.
excellent reported at 24 hours were significantly higher in the IV acetaminophen plus PCA morphine arm over the placebo plus PCA morphine arm (40.8% vs 23.1%, \( P=0.004 \)).\(^{16} \)

A recent 2013 publication of a pooled analysis of patient satisfaction scores from 5 RCTs evaluated IV acetaminophen in the acute postoperative setting.\(^{26} \) The analysis included patient-level data from the 2 pivotal trials for OFIRMEV, as well as FDA registrational studies in the following surgery types: open abdominal gynecological surgery, vaginal hysterectomy, and hip arthroplasty. In each of these studies, patient satisfaction was measured using a 4-point categorical rating scale. The end points were excellent satisfaction (primary) and good or excellent satisfaction at 24 hours after first administration of study drug.\(^{26} \)

The analysis concluded that implementing a multimodal analgesic regimen that includes IV acetaminophen results in significantly greater patient satisfaction. Patients who received IV acetaminophen were more than twice as likely as those who received placebo to report excellent satisfaction with study treatment (32.3% vs 15.9%, respectively; \( P<0.001 \)).\(^{26} \)

### Clinical Safety of OFIRMEV

The safety of IV acetaminophen has been established by a clinical trial data set comprised of 1,020 adult patients, including 37.3% (n=380) who received 5 or more doses, and 17% (n=173) who received more than 10 doses. Most adult

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\( ^{a} \)Note: Opioid consumption reduction is highly dependent on clinical trial design, and the clinical consequence of any amount of opioid consumption may not have been evaluated or demonstrated in any given trial.
patients, 86.9% (n=886), were treated with IV acetaminophen 1 g every 6 hours. A total of 13.1% (n=134) received IV acetaminophen 650 mg every 4 hours. The most common treatment-emergent AEs occurring in at least 3% of adult patients treated with IV acetaminophen and at a greater frequency than placebo in repeated-dose studies were nausea, vomiting, headache, and insomnia (Table 1). Health care practitioners should be aware that the antipyretic effects of IV acetaminophen may mask fever in patients treated for postsurgical pain.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product.

Safety data from a pooled analysis of 5 repeated-dose, placebo-controlled clinical studies involving adults demonstrate that when dosed appropriately, the incidence of liver function enzyme elevations was comparable to that seen with placebo (Table 2).

**Recommended Dosing of OFIRMEV**

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. For adults and adolescents weighing 50 kg or more, the recommended dosage is 1,000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of 1,000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen not to exceed 4,000 mg in 24 hours (Table 3).

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors that could result in accidental overdose and death. In particular, ensure that the dose in milligrams and milliliters is not confused, the dosing is based on weight for patients under 50 kg, infusion pumps are properly programmed, and the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

Dosing for children at least 2 years of age and adolescents and adults weighing less than 50 kg is listed in Table 3. For doses less than 1,000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container (eg, glass bottle, plastic IV container, or syringe) before administration. Once the vacuum seal of the OFIRMEV glass vial has been penetrated, or the contents have been transferred to another container, the dose must be administered within 6 hours.

**Conclusion**

Although there have been many developments and an increased emphasis on pain management over the past 2 decades, relatively little has changed with regard to the incidence of postsurgical pain or of patients’ perception of their pain management. Postoperative pain continues to be inadequately controlled. Because of this, opioid monotherapy should no longer be viewed as an adequate strategy for postoperative pain management.

Multimodal analgesia represents a shifting paradigm in perioperative pain management and has garnered the support of numerous professional organizations, including the ASA, ASPMN, AHRQ, and The Joint Commission. The ASA guidelines recommend that, unless contraindicated, acetaminophen, COXIBs, or NSAIDs be considered as part of a multimodal analgesic regimen.
Surgery, opioids, anesthesia, preoperative fasting, and postoperative stress can all work together in the immediate postoperative period to produce a profound gastroparesis and delayed gastric emptying. These factors should be taken into consideration when determining the appropriate route of analgesic administration.

IV acetaminophen is well suited for use in a multimodal analgesic regimen, with unique properties including rapid onset, established safety profile, and reduction in pain and fever. Include OFIRMEV as a foundational agent when establishing and implementing a multimodal analgesic regimen on standing orders in general surgery. Initiate analgesia with OFIRMEV preoperatively with the aim of improving pain relief and significantly reducing opioid use.

OFIRMEV is the first and only agent in the class of IV nonopioid, non-NSAID analgesics approved in the United States. As a foundational agent within a perioperative multimodal analgesic regimen, OFIRMEV improves pain relief, reduces opioid consumption, and increases patient satisfaction with pain treatment in the perioperative setting.

### Table 2. Peak ALT/AST Value Post-Baseline for Patients in 5 Pooled, Repeated-Dose, Placebo-Controlled Studies in Adults

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

**ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal

Based on reference 16.

* 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.

### Table 3. Recommended Dosing of OFIRMEV

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Given Every 4 h</th>
<th>Dose Given Every 6 h</th>
<th>Maximum Single Dose</th>
<th>Maximum Total Daily Dose of Acetaminophen By All Routes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (≥13 y) weighing ≥50 kg</td>
<td>650 mg</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
<td>4,000 mg in 24 h</td>
</tr>
<tr>
<td>Adults and adolescents (≥13 y) weighing &lt;50 kg and Children (2-12 y)</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 3,750 mg)</td>
</tr>
</tbody>
</table>

Based on reference 13.
Case Study 1

A healthy 70-year-old male found to have a large cecal polyp in a previous colonoscopy.¹

Sonia Ramamoorthy, MD, FACS, FASCRS

The polyp was removed and the pathology report was consistent with a villous adenoma. The patient returned for a follow-up colonoscopy in 2013; he was found to have a recurrent 3-cm polyp in the same location. The polyp was partially removed and pathology showed a villous adenoma with high-grade dysplasia. It was recommended that he undergo right hemicolectomy. The patient was seen in a surgery clinic and it was determined that he would benefit from a laparoscopic-assisted right hemicolectomy.

As part of the institution’s enhanced bowel recovery protocol, the patient was counseled about early ambulation, limiting narcotic intake, alternative pain medications, and he was given preoperative gabapentin (300 mg). The patient also underwent preoperative transversus abdominis plane block with 20 mL of bupivacaine one-fourth strength with epinephrine. The patient underwent an uneventful laparoscopic-assisted right hemicolectomy, and per protocol, 1 g of OFIRMEV was administered before skin closure. The patient was given one-fourth strength bupivacaine one-fourth strength with epinephrine. The patient underwent an uneventful laparoscopic-assisted right hemicolec- tomy, and per protocol, 1 g of OFIRMEV was administered before skin closure. The patient was given one-fourth strength bupivacaine hydrochloride injection into the wound. The surgery was approximately 2 hours in duration. The anastomosis was performed extracorporeally and the extraction site was 4 cm periumbilically.

Postoperatively, he was given 15 mg IV ketorolac every 6 hours and 1 g of OFIRMEV every 6 hours, not to exceed 4 doses in a 24-hour period. He was continued on gabapentin 300 mg every 8 hours. IV morphine sulfate 2 mg was available as needed every 2 hours for severe breakthrough pain. On the day of surgery, he was ambulating in the halls and reported pain scores of 0 to 2 (VAS). He was started on clear liquids. The patient reported an uneventful night, and on postoperative day (POD) 1, he passed flatus in the morning. He continued to ambulate throughout the day. His medications were continued and his pain scores remained at 0. By the evening of POD 1, the patient’s diet was advanced and plans were made for discharge the following day. The patient was discharged POD 2 following a bowel movement. He requested only oral ibuprofen and oral acetaminophen on discharge for pain. The patient’s total morphine intake during hospitalization was 2 mg given immediately postoperatively in the post-anesthesia care unit.

The patient was seen in clinic POD 14 for a follow-up visit. His wounds had healed adequately and he reported minimal pain since discharge that was adequately treated with oral acetaminophen. His activities were normal except for the surgical restrictions, and his final pathology report was consistent with villous adenoma with high-grade dysplasia.

Case Study 2

A 34-year-old female presents with a long history of morbid obesity.⁰

Anthony Gonzalez, MD

The patient has failed multiple medical attempts at weight loss, including diet, exercise, pharmacologic therapy, and holistic measures. She presented to the bariatric surgeon for evaluation for weight loss surgery, specifically sleeve gastrectomy.

On evaluation by the bariatric surgeon, she was found to have a past medical history of obstructive sleep apnea, treated with a continuous positive airway pressure mask during sleep, and fibrocystic breast disease. Her social history consisted of rare tobacco use and social alcohol consumption.

Her weight at the time of the office visit was 135 kg and her height was 66 inches; this calculated to a BMI of 48 kg/m². After discussing the diagnosis of morbid obesity and its medical, social, and psychological implications with the patient, the options for weight loss surgery were reviewed. The patient was offered 3 bariatric procedure options: adjustable gastric band, gastric sleeve, and gastric bypass. After careful discussion, both the patient and the surgeon agreed that the best bariatric procedure would be a robotic sleeve gastrectomy, along with a robotic hiatal hernia repair and upper endoscopy.

Before the procedure, the patient was given deep vein thrombosis prophylaxis, antibiotics, and 1 g of OFIRMEV. Via 4 laparoscopic incisions 5 to 12 mm in size, a robotic sleeve gastrectomy was created over a 36 French bougie. The staple line was oversewn. The hiatal hernia was repaired with non-absorbable sutures. The upper endoscopy was completed at the end of the procedure. The duration of the procedure was 1 hour and 23 minutes.

The patient was transferred to the recovery room and postop- erative orders were completed. They included 1 g of OFIRMEV every 6 hours, 30 mg of ketorolac every 8 hours, and 0.5 to 1.0 mg of hydromorphone every 3 hours as needed by the patient. The initial pain assessment score in the recovery room was a 7/10 (based on a 10-point VAS). The patient received 2 mg of IV hydromorphone during the night after surgery. Later that night the patient received her second dose of OFIRMEV (1 g); the pain score 32 minutes after that dose was 4/10.

On POD 1, the patient received her third dose of 1 g of OFIRMEV and the pain score was measured 30 minutes later and found to be 0/10. The last dose of OFIRMEV was given later on POD 1, as was 30 mg of ketorolac; the pain score 30 minutes after administration was 4/10. A total of 2 mg of IV hydromorphone was given to the patient on POD 1.

The patient ambulated 50 yards on the surgical day and more than 200 yards on PODs 1 and 2. She was discharged on POD 2.

¹Note: These case studies are intended only to provide health care professionals with examples of the use of OFIRMEV (acetaminophen) injection in the treatment of the specified patients. The outcomes described may not be representative of, and may differ significantly from, outcomes that may be obtained in treating other patients. These case studies are not intended to provide specific treatment advice, recommendations, or opinions, and should not replace a clinician’s judgment with respect to the treatment of any particular patient.
IMPORTANT RISK INFORMATION

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- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death. Do not exceed the maximum recommended daily dose of acetaminophen. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products. Dosing errors could result in accidental overdose and death.
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min).
- Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal.
- Hypersensitivity and anaphylaxis associated with the use of acetaminophen have been reported. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus.
- The antipyretic effects of OFIRMEV may mask fever.

ADVERSE REACTIONS

- Serious adverse reactions may include hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.
- Common adverse reactions in adults include nausea, vomiting, headache, and insomnia. Common adverse reactions in pediatric patients include nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Pregnancy Category C. OFIRMEV should be given to a pregnant woman only if clearly needed.
- Breast Feeding: While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration.
- Pediatrics: The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.
References


HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OFIRMEV (acetaminophen) Injection
Initial U.S. Approval: 1951

WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product (see WARNINGS).

INDICATIONS AND USAGE

OFIRMEV (acetaminophen) injection is indicated for the treatment of:

- Management of mild to moderate pain (1)
- Management of moderate to severe pain with adjunctive analgesics (1)
- Reduction of fever (1)

DOSEAGE AND ADMINISTRATION

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

OFIRMEV should be administered only as a 15-minute intravenous infusion. (2.1, 2.2)

Adults and Adolescents Weighing 50 kg and Over:

- 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:

- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:

- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

DOSE FORMS AND STRENGTHS

- Injection for intravenous infusion.
- Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL). (3)

CONTRAINDICATIONS

Acetaminophen is contraindicated:

- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation. (4)
- In patients with severe hepatic impairment or severe active liver disease. (4)

WARNINGS AND PRECAUTIONS

- Administration of acetaminophen in doses higher than recommended by all routes of administration and from all acetaminophen-containing products including combination products may result in hepatic injury, including the risk of liver failure and death. (5.1)
- Do not exceed the maximum recommended daily dose of acetaminophen (by all routes of administration and all acetaminophen-containing products including combination products). (5.1)
- Take care when prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death. (5.3)
- 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). (5.1)
- Discontinue OFIRMEV immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2, 5.4)

ADVERSE REACTIONS

The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients and nausea, vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cadence Pharmaceuticals Inc. at 1-877-647-2239 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. (7.1)

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. (7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. There are no studies of intravenous acetaminophen in pregnant women. Use only if clearly needed. (8.1)

Nursing Mothers: Caution should be exercised when OFIRMEV is administered to a nursing woman. (8.3)

Children: (8.4)

Recommended Dosage of OFIRMEV in children 2 to 12 years is supported by evidence from adequate and well-controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)

Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)

Hepatic Impairment: OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)

Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

OVERDOSAGE

10. OVERDOSAGE

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12. CLINICAL PHARMACOLOGY

12.1 Pharmacokinetics

12.3 Pharmacokinetics

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*Sections or subsections omitted from the full prescribing information are not listed.

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15. HOW SUPPLIED/STORAGE AND HANDLING

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product (see WARNINGS).

1 INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for:

- the management of mild to moderate pain
- the management of moderate to severe pain with adjunctive opioid analgesics
- the reduction of fever

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents who weigh 50 kg and above. Calculated maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen.

Exceeding the maximum mg/kg daily dose of acetaminophen as described in Tables 1 and 2 may result in hepatic injury, including the risk of liver failure and death. To avoid the risk of overdose, ensure that the total amount of acetaminophen from all routes and from all sources does not exceed the maximum recomended dose.

2.2 Recommended Dosage: Adults and Adolescents

Adults and adolescents weighing 50 kg and over: the recommended dosage of OFIRMEV is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Adults and adolescents weighing under 50 kg: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day (includes all routes of administration and all acetaminophen-containing products including combination products).
2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

Table 2: Dosing for Children

<table>
<thead>
<tr>
<th>Age group</th>
<th>Dose given every 4 hours</th>
<th>Dose given every 6 hours</th>
<th>Maximum single dose</th>
<th>Maximum total daily dose of acetaminophen (by all routes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 2 to 12 years of age</td>
<td>12.5 mg/kg</td>
<td>15 mg/kg</td>
<td>15 mg/kg (up to 750 mg)</td>
<td>75 mg/kg in 24 hours (up to 7350 mg)</td>
</tr>
</tbody>
</table>

2.4 Instructions for Intravenous Administration

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

For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV vial and place the measured dose in a separate empty, sterile container (e.g. glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL vial of OFIRMEV is not intended for use in patients weighing less than 50 kg. OFIRMEV is a single-use vial and the unused portion must be discarded.

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

3 DOSAGE FORMS AND STRENGTHS

OFIRMEV is a sterile, clear, colorless, non-pyrogenic, preservative-free, isotonic formulation of acetaminophen intended for intravenous infusion. Each 100 mL glass vial contains 1000 mg acetaminophen (10 mg/mL).

4 CONTRAINDICATIONS

Acetaminophen is contraindicated:
- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease [see WARNINGS AND PRECAUTIONS (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death [see OVERDOSE (10)]. Do not exceed the maximum recommended daily dose of acetaminophen [see DOSAGE AND ADMINISTRATION (2)]. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min) [see USE IN SPECIFIC POPULATIONS (8.5, 8.7)].

5.2 Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.3 Risk of Medication Errors

Take care when prescribing, preparing, and administering OFIRMEV (acetaminophen) injection in order to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:
- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits [see DOSAGE AND ADMINISTRATION (2)].

5.4 Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Hepatic Injury [see WARNINGS AND PRECAUTIONS (5.1)]
- Serious Skin Reactions [see WARNINGS AND PRECAUTIONS (5.2)]
- Allergy and Hypersensitivity [see WARNINGS AND PRECAUTIONS (5.4)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Adult Population

A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 3. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

Pediatric population

A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent
adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=355) that occurred with an incidence of at least 1%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singleton 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 (5%) 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.

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Labor and Delivery

There are no adequate and well-controlled studies with OFIRMEV during labor and delivery; therefore, it should only be used if the potential benefit-risk assessment.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages younger than 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age. [see DOSAGE AND ADMINISTRATION - Recommended Dosage: Children (2.3) and PHARMACOKINETICS (12.3)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% percent were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease. Therapy should be used with caution in patients with hepatic impairment or active liver disease [see WARNINGS AND PRECAUTIONS (5.1), CLINICAL PHARMACOLOGY (12)]. A reduced total daily dose of acetaminophen may be warranted.

8.7 Patients with Renal Impairment

OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of N-acetylcysteine (NAC) for intravenous administration. OFIRMEV is a sterile, clear, colorless, non pyrogenic, isotonic formulation of N-acetylcysteine (NAC) for intravenous administration. OFIRMEV is a sterile, clear, colorless, non pyrogenic, isotonic formulation of N-acetylcysteine (NAC) for intravenous administration.

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

10 OVERDOSAGE

8.5 Geriatric Use

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

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies. Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple
doses of oral acetaminophen.

12.3 Pharmacokinetics

Distribution

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration (Cmax) occurs at 30.Image not found. The doses were studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

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

Pharmacokinetic parameters of OFIRMEV (AUC, Cmax, terminal elimination half-life [T1/2], systemic clearance [CL], and volume of distribution at steady state [Vss]) following administration of a single intravenous dose of 15 mg/kg for the pediatric population and 1000 mg in adults are summarized in Table 4.

Table 4: OFIRMEV Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Subpopulations</th>
<th>AUC (µg × h/mL)</th>
<th>Cmax (µg/mL)</th>
<th>T1/2 (h)</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 ± 1.2</td>
<td>0.2 ± 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 ± 20</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 ± 19</td>
<td>31 ± 9</td>
<td>2.9 ± 0.7</td>
<td>0.29 ± 0.09</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Adults</td>
<td>43 ± 21</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>

The pharmacokinetic exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

Metabolism and Excretion

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: Conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450 enzyme pathway, primarily CYPP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). With therapeutic doses, NAPQI undergoes rapid conjugation with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHD, based on a body surface area comparison).

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosom aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of fertility

In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

14 CLINICAL STUDIES

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours compared to placebo.

Pain Study 2 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg every 6 hours or 650 mg every 4 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Patients receiving OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

14.2 Adult Fever

The efficacy of OFIRMEV 1000 mg in the treatment of adult fever was evaluated in one randomized, double-blind, placebo-controlled clinical trial. The study was a 6-hour, single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated through 6 hours in comparison to placebo. The mean temperature over time is shown in Figure 1.