Formulary Review: **Ofirmev®** **Reviewed: March 2011**
Generic Name: **Acetaminophen, IV**
Manufacturer: **Cadence Pharmaceuticals**
FDA Approval: **November 2010**
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Executive Summary

Introduction

Opioids remain the agents of choice for severe pain. However, they are associated with a variety of unwanted side effects including sedation, nausea, vomiting, constipation, cognitive impairment and respiratory depression. Non-opioid analgesics are commonly used alone or as adjuncts to opioid based analgesia to treat moderate to severe pain. Intravenous administration of analgesics is the preferred route in the immediate post-operative period, especially in certain patient populations. The U.S. Food and Drug Administration has recently granted marketing approval for Ofirmev (acetaminophen), the first and only intravenous formulation of acetaminophen to be approved for management of mild to moderate pain, moderate to severe pain with opioid analgesia, and reduction of fever.

Pharmacology/Pharmacokinetics

Acetaminophen acts by inhibiting prostaglandin synthesis in the central nervous system and blocking pain impulse generation via the COX enzyme. Ofirmev has been shown to achieve higher Cmax (70% higher) and earlier Tmax (30 min earlier) at the end of the 15 minute infusion than oral or rectal formulations with less intrasubject variability. The rapid CSF penetration and earlier and higher Cmax observed with Ofirmev appear to be responsible for its early onset and peak efficacy versus oral or rectal acetaminophen. The exposure of Ofirmev observed in children and adolescents is similar to adults, but higher in neonates and infants. Acetaminophen is primarily metabolized by the liver and its metabolites are mainly excreted in the urine

Clinical Efficacy

There were two main studies evaluating the safety and effectiveness of Ofirmev in the treatment of pain, and one study evaluating Ofirmev in the treatment of fever.

In a study of 101 orthopedic patients undergoing hip or knee replacement surgery, Ofirmev 1000 mg every six hours was statistically superior to placebo for the reduction of pain intensity over 24 hours ($p<0.01$) with significantly reduced morphine consumption (33% over 24 hours, $p<0.01$). Patients who received Ofirmev and required rescue analgesia had a significant longer elapsed time to rescue therapy ($p<.001$). PCA morphine consumption was lower in the Ofirmev group than in the placebo group representing a 33% reduction in opioid consumption. Ofirmev demonstrated a significant reduction in pain intensity over 24 hours compared to placebo ($p<0.02$).

The efficacy of Ofirmev 1000 mg in the treatment of adult fever was evaluated in two 6-hour, endotoxin-induced fever studies in 141 healthy adult males. Ofirmev 1000mg demonstrated a rapid onset of action and statistically significant temperature differences from baseline vs. placebo observed 15 minutes after completing infusion ($P=0.0085$).

Ofirmev was studied in 355 pediatric patients in two active controlled trials evaluating pain and fever and three open label safety and pharmacokinetic trials in children ranging 1month to 12 years.

An analysis of four single dose and 4 multiple dose studies demonstrated the risk of hepatoxicity with repeated doses of IV acetaminophen (1g every 6 hours up to 48 hours) may be no different than placebo.

Adverse Drug Reactions/ Drug Interactions

The most common side effect reported with Ofirmev was nausea (34%), vomiting (15%), headache (10%), and insomnia (7%). The primary safety concern with acetaminophen is its potential hepatic toxicity when used at doses higher than 4g/day. Therefore, caution should be used in patients with hepatic impairment, alcoholism, malnutrition, or severe renal impairment (Crcl <30 ml/min). Substances that induce CYP2E1 may alter the metabolism of acetaminophen and increase the risk

	of hepatotoxicity. A dose of 4000mg/day has been shown to interact with warfarin by increasing its INR.
Drug Interactions	It is a weak inhibitor of CYP2D6, but has not been found to inhibit any of the other CYP enzymes.
Dosage & Administration	Ofirmev is an injection for intravenous infusion where each 100ml glass vial contains 1000mg of acetaminophen. It should be given as a single or repeated dose and administered as a 15min infusion. Adults and adolescents weighing ≥50kg should be given 1000mg every 6 hours or 650 mg every 4 hours to a maximum of 4000mg per day. Adults and adolescents <50kg or children 2 to 12 years of age should receive 15mg/kg every 6 hours or 12.5 mg/kg every four hours to a maximum of 75mg/kg per day.
Summary	Ofirmev is an acetaminophen intravenous injection indicated for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever. Clinical trials have shown adequate pain relief, reduced opioid consumption, improved patient satisfaction, and effective fever reduction.
Formulary Status	**Non-formulary**