Pediatric Safety Review of OFIRMEV® (acetaminophen) Injection

Mike Royal, MD
VP, Clinical Development
& Medical Affairs

cadence™ PHARMACEUTICALS

- Cadence welcomes the opportunity to share the pre-approval and post-marketing safety experience with OFIRMEV (IV acetaminophen) with the Committee and the FDA

- Cadence supports FDA efforts to mitigate the risk of medication errors resulting in acetaminophen overdose

cadence™ PHARMACEUTICALS

Introduction

- 10 years of world-wide safety experience with IV acetaminophen incorporated in US NDA
  - allowed Cadence to work with FDA to structure OFIRMEV label to mitigate the risk of medication errors and acetaminophen overdose
- US label differs in several important ways from that of foreign IV acetaminophen labels
- Educational program designed and implemented to:
  - assist with selection of appropriate OFIRMEV dose
  - alert health care professionals not to exceed the daily maximum acetaminophen dose by any route
    - 4000 mg for adults and adolescents weighing 50 kg or more
    - for children, a weight-based 75 mg/kg daily maximum dose

IV Acetaminophen: Pediatric Postmarketing Safety Experience

- Estimated IV acetaminophen exposure:
  - US - 1.4 to 1.8 million patients
  - World-wide - >36 million patients
- Safety reports of medical errors resulting in pediatric acetaminophen overdose since 2006:
  - 27 reports involving pediatric patients
  - Only one from US experience (8 month old child administered 113 mg/kg OFIRMEV)
  - Up to 20-fold overdoses of IV acetaminophen occurred
  - No correlation between mg/kg overdose and adverse outcome
- Foreign medication errors fall into the following categories:
  - Most common (≈ 50%) are confusion as to appropriate dose or clear mistakes (kg vs. lbs; single vs. daily dose)
  - 10-fold overdose (mg vs. mL confusion) were common (≈ 1/3rd)
  - Administration of entire “pediatric” vial content (50 mL)
  - Incorrect administration route – e.g., intra-arterial or epidural
  - Concomitant oral and IV dosing was rare

IV Acetaminophen: Pediatric Postmarketing Safety Experience

- 18/27 of the pediatric overdose cases are in the < 2 years old category – not currently indicated in the US
  - Most dose confusion outside the US appears to be in neonates and young infants:
    - approved IV dose (7.5 mg/kg) is different than recommendations in authoritative texts (e.g. Harriet Lane, 15 mg/kg for PO/PR dosing) or published literature (loading dose up to 20 mg/kg and interval dose of 15 mg/kg)
  - To date, OFIRMEV use in < 2 age group appears to be minimal
    - lack of dosing guidance for any route of administration
    - PK section of OFIRMEV label suggest a 50% or 33% dose reduction in neonates and infants, respectively

OFIRMEV Prescribing Information

OFIRMEV
(acetaminophen) injection

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

INDICATIONS AND USAGE

OFIRMEV (acetaminophen) injection is indicated for the
- Management of mild to moderate pain (1)
- Management of moderate to severe pain with adjunctive opioid analgesics (1)
- Reduction of fever (1)

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 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

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

Children:
- Children ≥ 2 to 12 years old: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. (5.1)
- Do not exceed the maximum recommended daily dose of acetaminophen. (5.1)
- 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 if symptoms associated with allergy or hypersensitivity 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, constipation, pruritus, agitation, and atelectasis in pediatric patients. (6.1)

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

DRUG INTERACTIONS

- Substa enzym acetam
- Chroni been s ratio (sodium

- Pregna acetam needed
- Nursin admin
- Pediat treatm in ped and ef than 2 well co pharm
- Geriat effecti subjec
- Hepati patient liver d with h
- Renal longer acetam

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death [*see OVERDOSAGE (10)*]. Do not exceed the maximum recommended daily dose of acetaminophen [*see DOSAGE AND ADMINISTRATION (2)*].

Maximum total daily dose of

the
from
ntainer

RMEV
ng less

than 50 kg.

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

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 administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15-minutes. Use aseptic technique when preparing OFIRMEV for intravenous infusion. Do not add other medications to the OFIRMEV vial or infusion device.

For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV vial and place the measured dose in a separate empty, sterile contain
contain
avoid t
of the
contain
is not
than 5

conditi
disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min) [*see USE IN SPECIFIC POPULATIONS (8.6, 8.7)*].

5.2 Allergy and Hypersensitivity

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

E REACTIONS

llowing serious adverse reactions are sewhere in the labeling:

: Injury [*see WARNINGS AND UTIONS (5.1)*]

and Hypersensitivity [*see WARNINGS RECAUTIONS (5.2)*]

Trial Experience

l trials are conducted under ditions, adverse reaction rates directly compared to rates in and may not reflect the rates

ients have received , including 37.3% e doses, and 17.0% han 10 doses. Most FIRMEV 1000 mg % (n=134) received urs.

t occurred in adult IRMEV or placebo rolled clinical trials a greater frequency Table 2. The most ult patients treated 5% and greater than ing, headache, and

Reactions Occurring frequency than Placebo e Studies

IRMEV N=402) n (%)	Placebo (N=379) n (%)
38 (34)	119 (31)
2 (15)	42 (11)
22 (5)	52 (14)
39 (10)	33 (9)
30 (7)	21 (5)

cy data is included in rs that the antipyretic er.

Observed During ies of OFIRMEV in Adults llowing additional treatment-emergent ctions were reported by adult subjects h OFIRMEV in all clinical trials 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 an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

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

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

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

Blood and lymphatic system disorders: anemia
Cardiac disorders: tachycardia
Gastrointestinal disorders: abdominal pain, diarrhea
General disorders and administration site conditions: injection site pain, edema peripheral, pyrexia
Investigations: hepatic enzyme increase
Metabolism and nutrition disorders: hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia
Musculoskeletal and connective tissue disorders: muscle spasm, pain in extremity
Nervous system disorders: headache
Psychiatric disorders: insomnia
Renal and urinary disorders: oliguria
Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pleural effusion, stridor, wheezing
Skin and subcutaneous tissue disorders: periorbital edema, rash
Vascular disorders: hypertension, hypotension

7 DRUG INTERACTIONS

7.1 Effects of other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

7.2 Anticoagulants

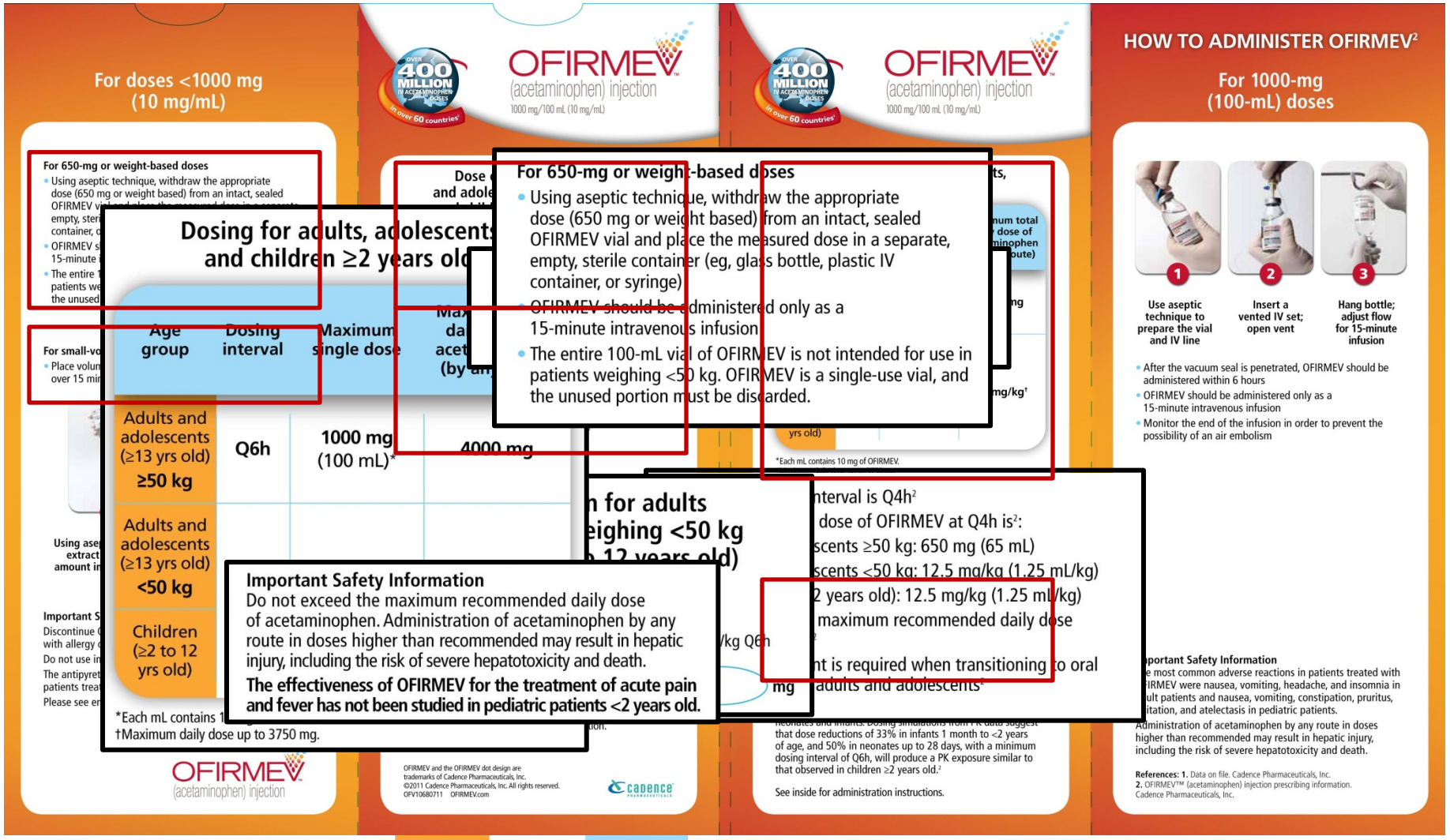
Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase

cadence™ PHARMACEUTICALS

OFIRMEV Educational Initiatives in use Since Launch

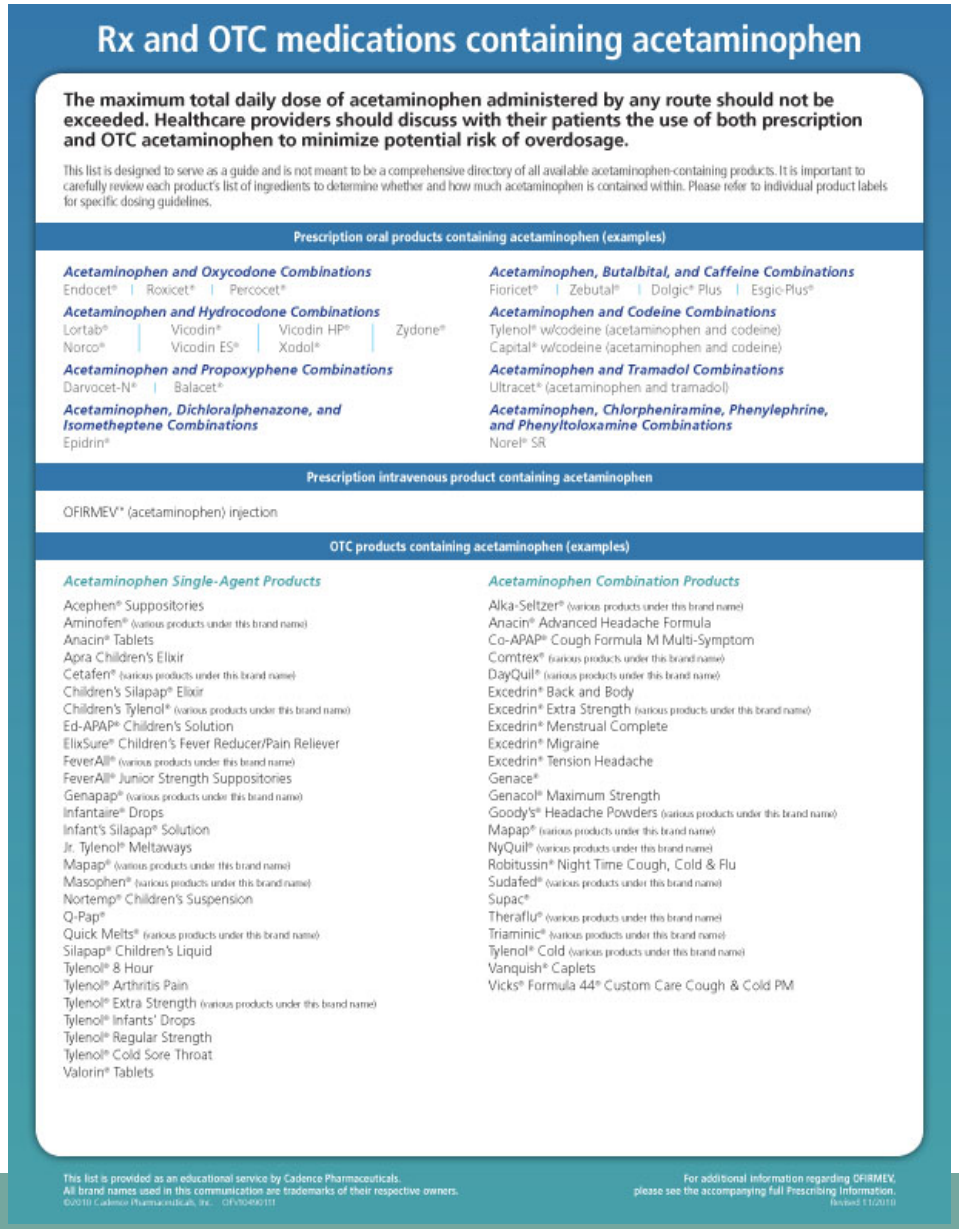
- Initial education efforts directed to healthcare practitioners designed to reinforce the importance of correct pediatric dose calculations and administration techniques
  - Appropriate use and administration instructions for all indicated age groups (video on OFIRMEV.com)
  - Dosing card: easy way to calculate the correct dose *in both mg/kg and in mL/kg* for all children (age 2 and older) and adults/adolescents under 50 kg weight
  - Reinforce label guidance with specific emphasis on the importance of adhering to acetaminophen maximum daily dose recommendations, *by any route of administration*
- Raise awareness of commonly used oral acetaminophen containing products
  - Posters and “tear-off” sheets
  - Referral to “knowyourdose.org” (Acetaminophen Awareness Coalition)
  - Medical Information letters and other educational materials on dosing and IV to oral transitions

OFIRMEV Educational Initiatives – Dosing Card



cadence™ PHARMACEUTICALS

OFIRMEV Educational Initiatives – Acetaminophen-Containing Oral Medications



Rx and OTC medications containing acetaminophen

The maximum total daily dose of acetaminophen administered by any route should not be exceeded. Healthcare providers should discuss with their patients the use of both prescription and OTC acetaminophen to minimize potential risk of overdosage.

This list is designed to serve as a guide and is not meant to be a comprehensive directory of all available acetaminophen-containing products. It is important to carefully review each product's list of ingredients to determine whether and how much acetaminophen is contained within. Please refer to individual product labels for specific dosing guidelines.

Prescription oral products containing acetaminophen (examples)

Acetaminophen and Oxycodone Combinations
Endocet® | Roxicet® | Percocet®

Acetaminophen and Hydrocodone Combinations
Lortab® | Vicodin® | Vicodin HP® | Zydone®
Norco® | Vicodin ES® | Xodol®

Acetaminophen and Propoxyphene Combinations
Darvocet-N® | Balacet®

Acetaminophen, Dichloralphenazone, and Isomethetpene Combinations
Epidrin®

Acetaminophen, Butalbital, and Caffeine Combinations
Fioricet® | Zebutal® | Dolgic® Plus | Esgic-Plus®

Acetaminophen and Codeine Combinations
Tylenol® w/codeine (acetaminophen and codeine)
Capital® w/codeine (acetaminophen and codeine)

Acetaminophen and Tramadol Combinations
Ultracet® (acetaminophen and tramadol)

Acetaminophen, Chlorpheniramine, Phenylephrine, and Phenyltoloxamine Combinations
Norel® SR

Prescription intravenous product containing acetaminophen

OFIRMEV® (acetaminophen) injection

OTC products containing acetaminophen (examples)

Acetaminophen Single-Agent Products
Acephen® Suppositories
Aminofen® (various products under this brand name)
Anacin® Tablets
Apra Children's Elixir
Cetafen® (various products under this brand name)
Children's Silapap® Elixir
Children's Tylenol® (various products under this brand name)
Ed-APAP® Children's Solution
ElixSure® Children's Fever Reducer/Pain Reliever
FeverAll® (various products under this brand name)
FeverAll® Junior Strength Suppositories
Genapap® (various products under this brand name)
Infantaire® Drops
Infant's Silapap® Solution
Jr. Tylenol® Meltaways
Mapap® (various products under this brand name)
Masophen® (various products under this brand name)
Nortemp® Children's Suspension
Q-Pap®
Quick Melts® (various products under this brand name)
Silapap® Children's Liquid
Tylenol® 8 Hour
Tylenol® Arthritis Pain
Tylenol® Extra Strength (various products under this brand name)
Tylenol® Infants' Drops
Tylenol® Regular Strength
Tylenol® Cold Sore Throat
Valorin® Tablets

Acetaminophen Combination Products
Alka-Seltzer® (various products under this brand name)
Anacin® Advanced Headache Formula
Co-APAP® Cough Formula M Multi-Symptom
Comtrex® (various products under this brand name)
DayQuil® (various products under this brand name)
Excedrin® Back and Body
Excedrin® Extra Strength (various products under this brand name)
Excedrin® Menstrual Complete
Excedrin® Migraine
Excedrin® Tension Headache
Genace®
Genacol® Maximum Strength
Goody's® Headache Powders (various products under this brand name)
Mapap® (various products under this brand name)
NyQuil® (various products under this brand name)
Robitussin® Night Time Cough, Cold & Flu
Sudafed® (various products under this brand name)
Supac®
Theraflu® (various products under this brand name)
Triaminic® (various products under this brand name)
Tylenol® Cold (various products under this brand name)
Vanquish® Caplets
Vicks® Formula 44® Custom Care Cough & Cold PM

This list is provided as an educational service by Cadence Pharmaceuticals.
All brand names used in this communication are trademarks of their respective owners.
©2010 Cadence Pharmaceuticals, Inc. OFV10490111

For additional information regarding OFIRMEV, please see the accompanying full Prescribing Information.
Revised 11/2010

cadence™ PHARMACEUTICALS

OFIRMEV Educational Initiatives – Day Surgery Discharge Instructions

Day surgery discharge instructions

For medications containing acetaminophen in adults weighing ≥50 kg

During your procedure, you were given acetaminophen 1000 mg (1 g) for pain control at _____ AM/PM.
If you need additional pain medication at home, take as directed by your physician.

Take _____ (checked below) no sooner than _____ AM/PM.

It is important that you do not exceed the maximum amount of acetaminophen, 4000 mg (4 g), in the remaining 24 hours.

☑	Medication	Acetaminophen amount per tablet	Total tablets remaining (acetaminophen amount)
☐	Tylenol® Regular Strength (acetaminophen tablets)[1]	325 mg	9 tablets (2925 mg)
☐	Tylenol® Extra Strength (acetaminophen tablets)[2]	500 mg	6 tablets (3000 mg)
☐	Tylenol® #3 (acetaminophen and codeine tablets)[3]	300 mg	10 tablets (3000 mg)
☐	Percocet® (5 mg/325 mg or 10 mg/325 mg) (acetaminophen and oxycodone tablets)[4]	325 mg	9 tablets (2925 mg)
☐	Norco® (acetaminophen and hydrocodone tablets)[5]	325 mg	9 tablets (2925 mg)
☐	Lortab® (acetaminophen and hydrocodone tablets)[6]	500 mg	6 tablets (3000 mg)
☐	Vicodin® (5 mg/300 mg) (acetaminophen and hydrocodone tablets)[7]	300 mg	8 tablets (2400 mg)
☐	Vicodin® (5 mg/500 mg) (acetaminophen and hydrocodone tablets)[7]	500 mg	6 tablets (3000 mg)

These instructions are designed to serve as a guide and are not meant to be a comprehensive directory of all available acetaminophen-containing products. It is important to review each product's list of ingredients to determine whether and how much acetaminophen is contained within. Please refer to individual product labels for specific dosing guidelines.

References: 1. Regular Strength Tylenol® [Directions for use]. Fort Washington, PA: McNeil Consumer Healthcare LLC; 2012. 2. Extra Strength Tylenol® [Directions for use]. Fort Washington, PA: McNeil Consumer Healthcare LLC; 2012. 3. Tylenol® with Codeine No. 3 [package insert]. Raritan, NJ: Ortho-McNeil Janssen Pharmaceuticals; 2011. 4. Percocet® [package insert]. Chadds Ford, PA: Endo Pharmaceuticals; 2011. 5. Norco® [package insert]. Corona, CA: Watson Pharma, Inc.; 2011. 6. Lortab® [package insert]. Smyrna, GA: UCB Pharma, Inc.; 2011. 7. Vicodin® [package insert]. North Chicago, IL: Abbott Laboratories; 2011.

For additional information regarding OFIRMEV® (acetaminophen) injection, please see full Prescribing Information.

OFIRMEV Additional Pediatric Presentations?

- Smaller volume vial
  - A 50 mL vial of IV acetaminophen 10 mg/mL is available for use in EU specifically for newborn infants, infants and toddlers and children < 33 kg
  - The smaller “pediatric” presentation has resulted in confusion that the vial was appropriate for all children, including neonates, resulting in overdose via administration of entire vial
  - Difficult to find a vial size that fits most pediatric doses and reduces overdose risk
  - Current approach in the US of removing product from vial and either putting into a separate sterile container or a syringe pump for small volumes appears to be the optimal approach
- More dilute concentration
  - Introduction of a diluted solution could result in volume overload in low bodyweight pediatric patients and a 2nd concentration may lead to more rather than less dosing confusion
  - Note that the 2009 & 2011 Advisory Committees discussing oral acetaminophen voted in favor of having one concentration of acetaminophen liquid and one concentration of oral pediatric acetaminophen products

Summary

- Cadence supports FDA efforts to mitigate the risk of medication errors resulting in acetaminophen overdose
- OFIRMEV label
  - highlights need to respect the max daily dose of acetaminophen by any route in all indicated age groups
  - Clearly states the risks of exceeding max daily dose
  - Gives clear administration instructions for small volume and pediatric use
- Cadence has introduced educational material reinforcing the OFIRMEV label and identifying common acetaminophen containing products
- Cadence does not support introduction of additional presentations or reduced concentrations of OFIRMEV as they will add confusion and increase the probability of dosing errors resulting in overdose

cadence™ PHARMACEUTICALS