Pediatric Focused Safety Review: Ofirmev™ (acetaminophen injection)

Pediatric Advisory Committee Meeting

September 11, 2012

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Outline

- Background Information
- Pediatric Studies
- Relevant Labeling
- Drug Use Trends
- Safety Review
  - Safety Issue Identified in the Literature
  - Adverse Event Review
  - Medication Error Review
- Summary

Background Drug Information

Ofirmev™ (acetaminophen injection)

- **Drug:** Ofirmev™(acetaminophen injection)
- **Formulation:** injection for intravenous use
- **Sponsor:** Cadence Pharmaceuticals
- **Original Market Approval:** November 2, 2010
- **Therapeutic Category:** non-salicylate antipyretic and non-opioid analgesic agent.

Background Drug Information, continued
Ofirmev™ (acetaminophen injection)

- **Indications (Patients 2 years and older)**:

  1. Management of mild to moderate pain

  2. Management of moderate to severe pain with adjunctive opioid analgesics

  3. Reduction of fever

- **Postmarketing Requirements:**

  Pharmacokinetic (PK), pharmacodynamic (PD) and efficacy study of IV acetaminophen for treatment of acute pain in patients 0 to 2 years.

Pediatric Studies
Ofirmev™ (acetaminophen injection)

Five pediatric Ofirmev™ trials performed:

- Two active-controlled and three open-label safety and pharmacokinetic (PK) trials.
- 355 patients were enrolled from birth to 16 years of age.
- No deaths reported.
- The most common adverse events (incidence ≥ 5%) in pediatric patients treated with Ofirmev™ were nausea, vomiting, constipation, pruritus, agitation and atelectasis.

Approval in pediatrics was supported by data from adults.

Data supported labeling for ages 2 years and above.

Relevant Labeling
Ofirmev™ (acetaminophen injection)

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage: Adults and Adolescents

50 kg and over: 1000 mg every 6 hours or 650 mg every 4 hours up to a maximum daily dose of 4000 mg per day.
Under 50 kg: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with maximum dose of 75 mg/kg per day.

2.3 Recommended Dosage: Children ≥ 2 to 12 years of age

15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum daily dose of 75 mg/kg per day.

4 CONTRAINDICATIONS

- Known hypersensitivity to acetaminophen or to excipients in the formulation.
- Severe hepatic impairment or severe active liver disease.

Relevant Labeling, continued
Ofirmev™ (acetaminophen injection)

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Acetaminophen in doses higher than recommended may result in hepatic injury.

Use caution in patients with hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment.

5.2 Allergy and Hypersensitivity

6 ADVERSE REACTIONS

6.1 Adverse reaction data from the clinical trials are provided for adult and pediatric patients.

7 DRUG INTERACTIONS

7.1 Effects of other Substances on Acetaminophen

7.2 Anticoagulants

Relevant Labeling, continued
Ofirmev™ (acetaminophen injection)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Information regarding the basis of approval in pediatrics provided. States that additional safety and PK data have been collected in pediatric studies across the full pediatric age range.

8.6 Patients with Hepatic Impairment

8.7 Patients with Renal Impairment

10 OVERDOSAGE

Includes recommendations on treatment

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

PK data provided for children (neonates to adolescents) and adults.

14 CLINICAL STUDIES

14.3 Pediatric Acute Pain and Fever

Pediatric Use
Ofirmev™ (acetaminophen injection)

Nationally estimated number of discharges and patients by patient age who had a hospital billing for Ofirmev™ from November 2010 through February 2012 in U.S. non-federal hospital inpatient and outpatient ER settings.

	Discharges	%	Patients	%
Total Ofirmev™	**76,756**	**100.0%**	**74,935**	**100.0%**
0-1 years	33	0.04%	33	0.04%
2-16 years	1,119	1.46%	1,119	1.49%
17+ years	75,596	98.49%	73,775	98.45%
Unknown Age	7	0.01%	7	0.01%

Source: IMS Health, Inpatient Healthcare Utilization System. November 2010 through February 2012. Data extracted May 2012.

Safety Issue from Literature
Ofirmev™ (acetaminophen injection)

"Intravenous Acetaminophen in the United States: Iatrogenic Dosing Errors"*

January 2012 article discusses 10 fold dosing errors in "small children" based on the EU experience.

- Ofirmev™ solution is 10 mg/mL.
- The dose is calculated in mg but may be erroneously given in mL.
- The authors suggest:
  - hospitals should be proactive, educating staff of the potential dosing error when Ofirmev™ is added to the hospital formulary.
  - treating according to the current guidelines for overdose but to consider treatment for overdoses of 150 mg/kg or greater.

*Dart, R and Rumack, B. *Pediatrics, 2012.* 129 (2): 349-353.

Safety Evaluations
Ofirmev™ (acetaminophen injection)

- Adverse Event Reporting System (AERS) Case Review:
  - Includes all reports regardless of causality submitted to AERS.
  - Only includes cases reported after drug approval.
- Division of Medication Error Prevention and Analysis (DMEPA) Review.
  - Includes multiple databases including AERS.
  - Focus is on dosing errors.
  - Includes cases reported prior to and after drug approval.

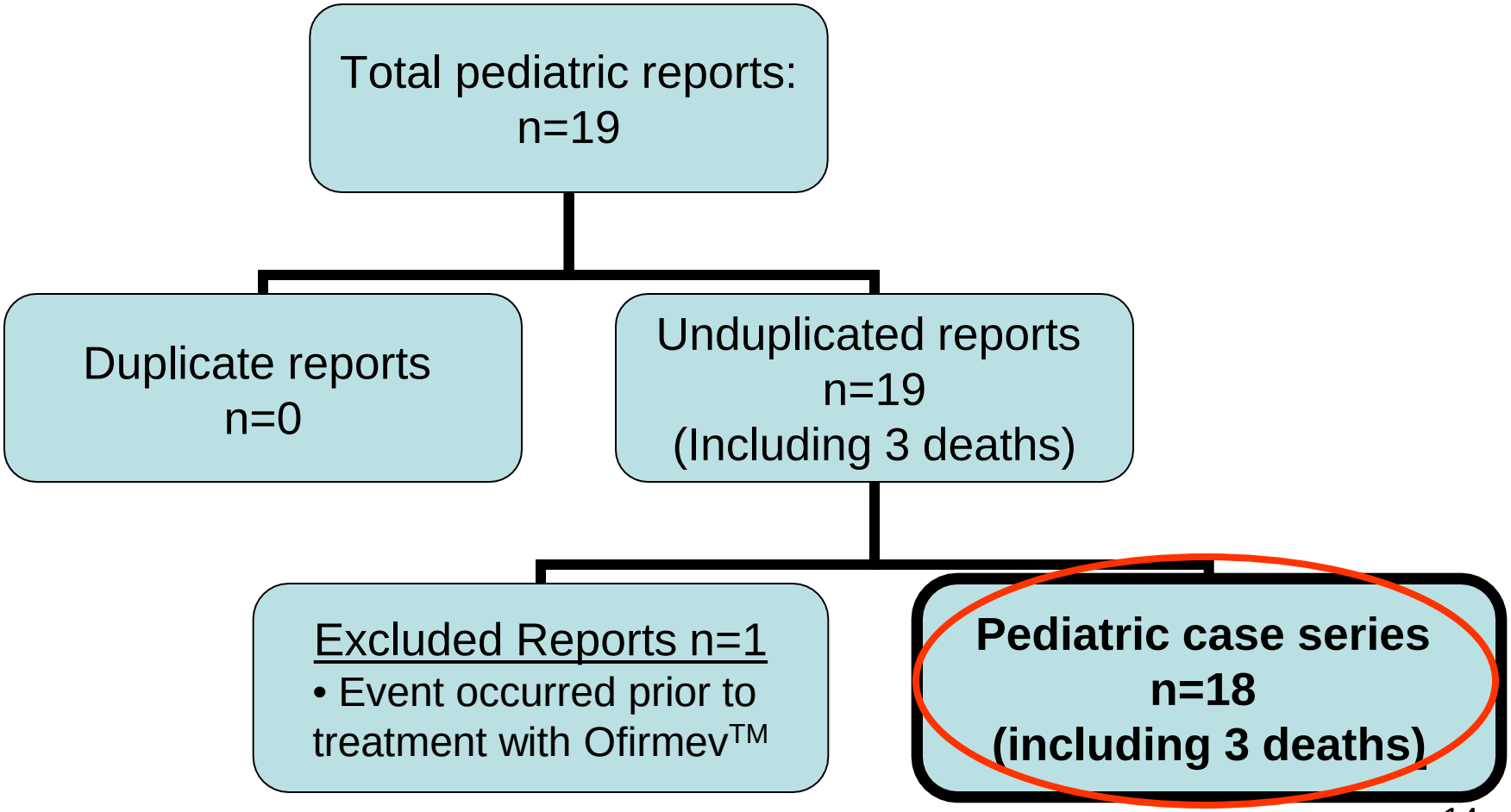
Adverse Event Reporting System Review

Total Number* of Ofirmev™ Adverse Event Reports (AERS) Since Pediatric Approval (11/2/10 to 3/31/12)

	All reports (US)^	Serious (US)**	Deaths (US)
Adults (≥ 17 yrs.)	74 (6)	72 (6)	14 (1)
Pediatrics (0-16 yrs.)	19 (0)	19 (0)	3 (0)
Unknown Age ***	12 (5)	11 (4)	3 (0)
All Ages	105 (11)	102 (10)	20 (1)

* May include duplicates and have not been assessed for causality.
^ US counts in parentheses.
**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
***No pediatric reports identified.

Pediatric Case Selection



Characteristics of Pediatric Cases Ofirmev™ (n=18)

- Age (n=18)
  - Birth - 1 month (n=2)
  - 1 month - < 2 years (n=5)
  - 2 - 5 years (n=4)
  - 6 - 11 years (n=4)
  - 12 - 16 years (n=3)

- Duration of Therapy (n=18)
  - < 24 hours (n=15)
    Note: At least 8 of 15 appeared to involve single doses
  - 7 days (n=1)
  - Unknown (n=2)

Deaths (n=3)
Ofirmev™ (acetaminophen injection)

- **20 month-old male died due to <u>cardiopulmonary arrest.</u>**
  - Patient with dialysis dependent renal insufficiency, hypertension and congenital nephrotic syndrome died one day after kidney transplantation.
  - Patient on multiple concomitant medications including IV acetaminophen.
- **5 day-old female, 34 weeks gestation, died from <u>septic shock</u> and <u>cardiopulmonary arrest.</u>**
  - Patient had RH disease and necrotizing enterocolitis.
  - Received 7 days of IV acetaminophen in addition to multiple concomitant medications.
- **9 year-old male with <u>fever</u> and <u>gastrointestinal (GI) bleeding</u> died after administration of anesthesia.**
  - Patient had Evans Syndrome (autoimmune hemolytic anemia and thrombocytopenia) and a recent history of sepsis.
  - Patient was given IV acetaminophen and then taken to surgery for abdominal pain and GI bleeding.

*Unlabeled events are underlined on this slide and subsequent slides.

Serious Non-Fatal Adverse Events Ofirmev™ (acetaminophen injection) (n=15)

Neurologic (n=6)

Hepatic (n=3)

Hematologic (n=3)

Cardiovascular (n=1)

Respiratory (n=1)

“Lack of effect” (n=1)

Serious Non-Fatal Adverse Events, continued Ofirmev™ (acetaminophen injection)

Neurologic: Convulsions (n=6)

- **Suspected/confirmed malaria in patients treated with IV acetaminophen (n=4).**
  - Concomitant use of quinine in 2 cases. Quinine is labeled for seizures.
- **Limited information (n=1).**
  - Convulsion while on IV acetaminophen. Quality of acetaminophen questioned due to precipitant in vial.
- **1 year-old child with H1N1 Influenza.**
  - Tonic-clonic seizures and skin eruptions after IV acetaminophen and ampicillin.
  - Ofirmev™ and ampicillin are labeled for hypersensitivity reactions, including urticaria, pruritus, and anaphylaxis.

Serious Non-Fatal Adverse Events, continued

Ofirmev™ (acetaminophen injection)

Hepatic (n=3):

- **5 month-old female post surgery for intussusception developed hepatic impairment after receiving 75 mg/kg of IV acetaminophen.**
  - N-acetylcysteine (NAC) was administered and the patient recovered.
- **10 month-old male with cerebral lipoma, seizures and fever developed cytolytic hepatitis after receiving 80mg (10mg/kg) IV acetaminophen.**
  - Concomitant medications included drugs associated with hepatic dysfunction, including sodium valproate which has a boxed warnings for hepatotoxicity.
- **4 year-old female with suspected pneumonia developed fulminant hepatitis after receiving 3 doses of IV acetaminophen at 50 mg/kg**
  - NAC was given and the patient recovered.

Serious Non-Fatal Adverse Events, continued

Ofirmev™ (acetaminophen injection)

Hematologic (n=3):

- **An 18 month-old male with possible sepsis, encephalitis and influenza developed elevated international normalized ratio (INR) and hemorrhage after receiving 240 mg of IV acetaminophen.**
  - Concomitant medications included acyclovir and phenytoin, both labeled for thrombocytopenia.
- **A 6 year-old female with post-operative bleeding had an elevated activated partial thromboplastin time and prothrombin time after receiving 400 mg IV acetaminophen.**
  - Concomitant medications included oral ibuprofen, labeled for hemorrhage, and heparin sodium, an anti-coagulant.
- **A 1 day-old female born at 33 weeks with hypoprothombinemia and neonatal jaundice after receiving two 75 mg/kg doses of IV acetaminophen.**
  - Treated with Vitamin K and NAC.
  - Reviewers of the case considered the jaundice was likely physiologic.

Serious Non-Fatal Adverse Events, continued

Ofirmev™ (acetaminophen injection)

Cardiovascular (n=1):

- **A 4 year-old with Acute Lymphoblastic Leukemia (ALL) with second-degree A-V block.**
  - Concomitant medications included potentially pro-arrhythmic medications (sufentanil and propofol) in addition to IV acetaminophen.

Respiratory (n=1):

- **A 15 year-old, undergoing wisdom tooth extraction, experienced respiratory arrest after IV acetaminophen, remifentanil hydrochloride, sevoflurane, and propofol were administered.**
  - Medications given for anesthesia were listed as the probable cause of the respiratory arrest.

Lack of Effect (n=1):

- **A 12 year-old with ulcerative colitis and toxic megacolon experienced lack of analgesic effect.**
  - Patient received IV acetaminophen, ketamine and diclofenac for pain.

Summary Pediatric Focused Safety Review Ofirmev™ (acetaminophen injection)

- This concludes the pediatric focused safety review of AERS reports.
- No US case reports were identified.
- Dosing errors were identified but there were no additional safety signals.

Medication Error Review

Intravenous Acetaminophen Medication Errors

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Office of Surveillance and Epidemiology

Overview

- Background Information
  - Ofirmev™ (U.S. product, approved 2010)
  - Perfalgan (Foreign product, approved 2002)
  - Focus of analysis
- Data Sources
- Results and Analysis
- Conclusions and Recommendations

Ofirmev™ and Perfalgan Product Similarities

- Indication
  - mild to moderate pain, fever reduction
- Concentration
  - 10 mg/mL
- Route
  - intravenous
- Frequency of administration
  - every 4 hours or 6 hours

Ofirmev™ and Perfalgan Three Key Differences

Key Difference	Ofirmev™	Perfalgan
Approved patient population	Indicated in adults and pediatric patients **two years and older**	Indicated in adults and pediatrics including **term newborn infants, infants, toddlers and children** weighing less than 10 kg.
How supplied	100 mL (1 gm) glass bottle	**50 mL* (500 mg)** and 100 mL (1 gm) glass bottle
Presentation of Dosing Information	Labeling provides dosing solely in **milligrams**.	Labeling includes dosing in both **milligrams and milliliters**.

* The 50 ml vial is restricted to term newborn infants, infants, toddlers and children weighing less than 33 kg.

Ofirmev™ (Acetaminophen) Injection		Perfalgan (Paracetamol) Injection	
Patient Age	**Dosing**	**Patient Weight**	**Dosing**
Adults and Adolescents (13 years and older) weighing ≥ 50 kg	1000 mg every 6 hours OR 650 mg every 4 hours	> 50 kg	1 g (i.e. 100 mL vial) Up to 4 times per day
Adults and Adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg every 4 hours OR 15 mg/kg every 6 hours	> 33 kg and < 50 kg	15 mg/kg (i.e., 1.5 mL solution per kg) Up to 4 times per day
Children > 2 years to 12 years	12.5 mg/kg every 4 hours OR 15 mg/kg every 6 hours	> 10 kg and < 33 kg	15 mg/kg (i.e., 1.5 mL solution per kg) Up to 4 times per day
No dosing provided below 2 years of age		< 10 kg*	7.5 mg/kg (i.e., 0.75 mL solution per kg) Up to 4 times per day

*No safety and efficacy data are available for premature neonates. There is limited data on the use of Perfalgan in neonates and infants < 6 months of age

U.S. Label

NDC 43825-102-01

OFIRMEV™

(acetaminophen) injection

1000 mg/100 mL

(10 mg/mL)

For Intravenous Use Only

Single Use Vial. Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing. Discard unused portion.

Rx Only

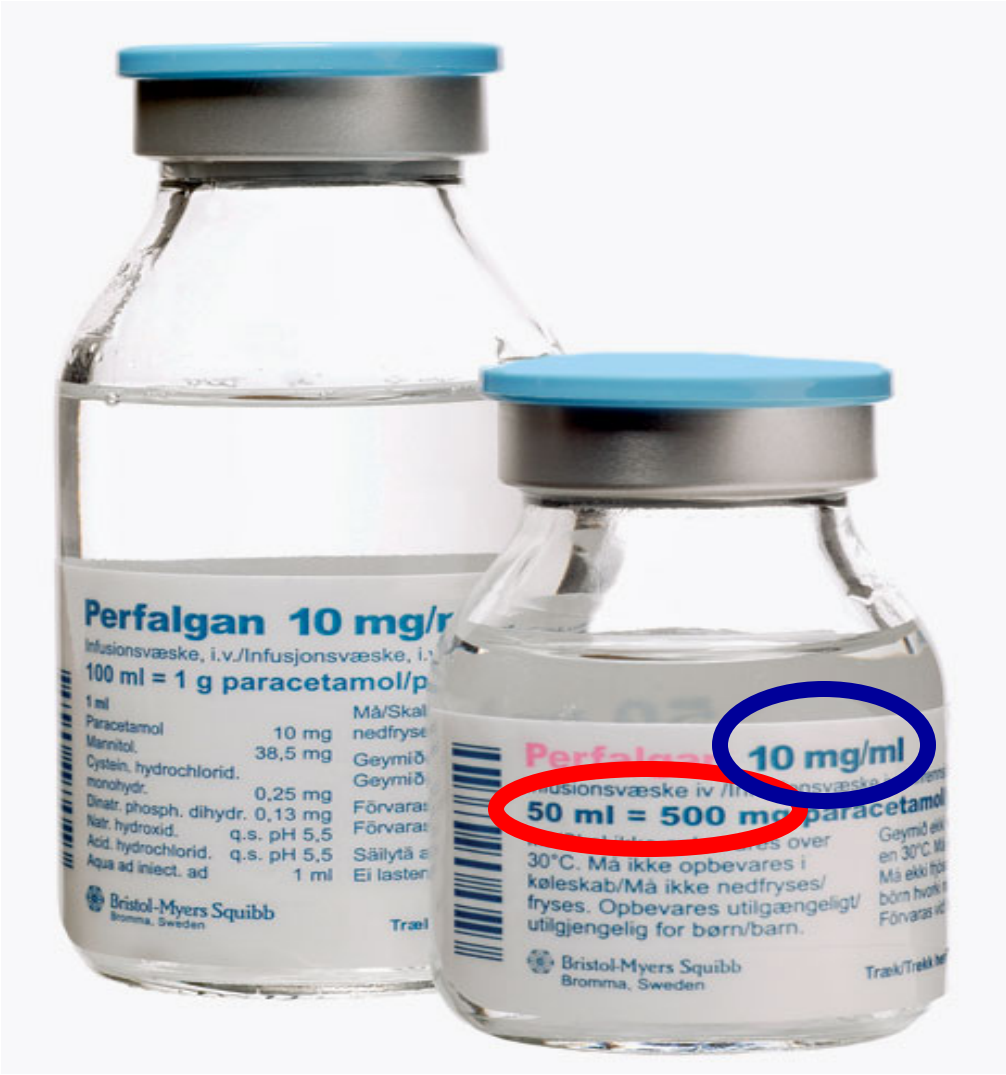
Store at controlled room temperature, 20°C to 25°C (68°F to 77°F).
Do not refrigerate or freeze.

Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, 10.4 mg dibasic sodium phosphate, anhydrous, USP. pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

See Package Insert for recommended dosage and Full Prescribing Information.

LOT [redacted] EXP [redacted]

Foreign Label



Focus of Analysis

- Ofirmev™ and Perfalgan Pediatric Errors
- Ofirmev™ and Perfalgan Adult Errors
- No time limitations for data search

Pharmacovigilance Data Sources

- Adverse Event Reporting System (AERS)
  - Voluntary, “spontaneous” reports from healthcare providers and consumers
  - Reports from
    - FDA MedWatch Program
    - Manufacturers
- Institute for Safe Medication Practices (ISMP)
  - Quantros MedMarx
  - Pennsylvania Patient Reporting System (PaPSRS)
  - ISMP MERP database

Pharmacovigilance Database Findings

27 cases Total
- 14 from AERS
- 13 from ISMP

10 Pediatric Cases
- 8 Foreign
- 2 U.S.

17 Adult Cases
- 4 Foreign
- 13 U.S.

Pediatric Medication Errors (n=10)

Table 1: Age and Origin of Medication Error Cases from AERS and ISMP		
	Domestic	**Foreign**
0 to 5 months	0	4
6 months to 1 year of age	0	2
2 to 16 years of age	1	2
Unknown*	1	0
Total Pediatric Cases (n=10)	**2**	**8**

Pediatric Overdoses (n=10)

- All ten patients received an overdose
- No deaths
- Seven cases reported hepatic impairment following administration of a single dose
- Majority were 10 fold dosing errors (n=6)
  - Doses reported up to 165 mg/kg

U.S. Pediatric Overdose Cases (n = 2)

- 25 kg child prescribed 250 *mg* dose (10 mg/kg). The infusion pump was programmed to deliver 250 *mL* (2500 mg) instead of 25 *mL* (250 mg) error was caught after the first 100 *mL* (1000 mg) given

- Database provider did not give permission to disclose details from the second case

Pediatric Adverse Events Reported

- Fulminant hepatitis (n = 1)
- Elevated liver function tests (n = 4)
- Hypo-prothrombinemia and neonatal jaundice (n = 1)
- Elevated International Normalized Ratio (n = 2)
- Elevated Acetaminophen (Paracetamol) level (n = 2)

Pediatric Treatment and Final Outcome

- **Treatment**
  - N-Acetylcysteine (n=5)
  - N-Acetylcysteine and vitamin K (n=2)
  - Not treated (n=1)
  - Unknown (n=2)

- **Final Outcome**
  - Patient Recovered (n=6)
  - Unknown (n=4)

Causes of Pediatric Overdose

- Dose not adjusted for patient's weight
- Intravenous and Oral product given consecutively
- Confusion between milligrams and milliliters
  - e.g., patient ordered 150 mg (15 mL) given 1500 mg (150 mL)
- Infusion pump misprogrammed

Literature Findings

- All pediatric foreign cases of overdose
  - Summary of data provided, no case specifics
  - Two unique cases identified
    - 1 death
- Majority overdoses occurred in neonates and infants less than 1 year of age
  - 10-fold overdose administered
  - Confusion between milligrams and milliliters

Literature Cases (n=2)

- Spain - young child prescribed 65 mg of intravenous paracetamol but was infused 65 mL (650 mg). The child was treated successfully with N-acetylcysteine.

- France – Death due to 10 fold overdose
  - The patient was administered 7 mL (70 mg) of paracetamol instead of 0.7 mL (7 mg)

Adult Error Cases (n = 17)

Table 2: Adult Medication Errors by Age and Origin		
	Domestic	**Foreign**
17 years to 30 years of age	0	2
31 years to 50 years of age	3	1
51 years to 73 years of age	6	1
Unknown*	4	0
Total Adult Cases (n=17)	**13**	**4**

***Although age not specified, we were able to determine the case involved an adult patient based on the information and dosing provided in the case narrative.**

Adult Cases (n=17)

- Majority cases describe actual administration of an overdose of acetaminophen/paracetamol (n=15)
- Near miss of overdose (n=1)
  - prescribed overdose caught by pharmacist prior to patient administration
- Wrong dilution of the correct dose that lead to administration of an underdose (n=1)
  - patient ordered 750 mg in 7.5 mL but received 750 mg in 75 mL (75 mg) x 3 doses

Adult Adverse Events Reported

- Hepatic failure (n = 2)
- Acute Liver Injury (n =1)
- Fulminant hepatitis (n = 1)
- Elevated liver function tests (n = 1)
- Unknown (n = 12)

Adult Treatment and Final Outcome

- **Treatment**
  - N-Acetylcysteine (n=3)
  - Unknown (n = 14)
- **Final Outcome**
  - Death (n=2)
  - LFT's remained high upon discharge (n = 1)
  - Unknown (n=14)

Causes of Adult Overdose (n=15)

- Total daily dose exceeds 4 grams in 24 hours (n=12)
  - IV acetaminophen/paracetamol and narcotic containing acetaminophen/paracetamol [e.g., Percocet]
  - IV and oral acetaminophen/paracetamol
  - IV acetaminophen/paracetamol given around the clock
- Dose not adjusted for the patient's weight (n=3)
  - e.g., patient weighed less than 50 kg but received 1 gram of intravenous acetaminophen
  - Resulted in 2 deaths

Adult Death Cases (n=2)

- United Kingdom - 68 year old given dose that was not weight based; death was due to renal and hepatic failure related to acetaminophen overdose (per autopsy).
- United Kingdom - 19 year old given dose that was not weight based. Patient weighed 35 kg and given twenty doses of 1000 mg paracetamol for 5 days rather than 525 mg. Cause of death stated to be paracetamol toxicity.

Conclusions

- Similar risk of error for U.S. pediatric population
  - 10 fold dosing errors
  - Milligram and milliliter confusion
  - Inappropriate doses based on weight

- Limited interventions to minimize risk

Interventions to Minimize Risk (1)

- Strengthen labeling
  - Bring awareness to errors
  - Revise Precautions and Dosage and Administration to strengthen link between total daily dose and hepatic injury
- Prescribe dose in milligram and milliliter
  - May provide redundancy and double check but may pose some risk in U.S.
  - Risk during transcription of orders or if healthcare providers may cross reference the wrong dose
  - May not address errors related to pump misprogramming

Interventions to Minimize Risk (2)

- Provide smaller vial size of 50 mL or less
  - May limit amount of medication given, ease burden for compounding
  - Impact may be limited since cases of overdose still occurred in foreign market where 50 mL vial is available

Summary of Safety Reviews

Ofirmev™ (acetaminophen injection) Summary of Safety Reviews

Summary:

- IV acetaminophen is approved for patients 2 years and older.
- Studies in patients <2 years of age are required as a postmarket requirement (PMR).
- The DMEPA review identified risk of accidental dosing errors in pediatric patients in the U.S market.
- The pediatric focused review of AERS did not identify any additional safety signals.

Ofirmev™ (acetaminophen injection) Summary of Safety Reviews

Recommendations:

- FDA recommends revising the DOSAGE AND ADMINISTRATION section – to include a statement that alerts prescribers to the dosing errors that have occurred in the pediatric population. For example:

" *Take care when prescribing and administering Ofirmev™ Injection, in order to avoid dosing errors in pediatrics due to confusion between mg and mL, weight based dosage miscalculations, and infusion pump misprogramming which could result in accidental overdose and hepatic injury. Take care to ensure the proper dose is communicated and dispensed.*"

Ofirmev™ (acetaminophen injection) Summary of Safety Reviews

Recommendations:

- FDA recommends strengthening the Ofirmev™ labeling in the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections to include the link of hepatic risk to the maximum daily dose of 4000 mg.
- FDA recommends continued, routine safety monitoring, including monitoring for dosing errors.

Questions for Committee

- Do you agree with FDA's labeling recommendations?
- Should the labeling of Ofirmev™ be revised to recommend dosing of acetaminophen in both mg and mL? Yes, No, Why
- Do you recommend development of smaller vial sizes in the U.S.? Yes, No, Why
- Is routine safety monitoring, which includes monitoring for dosing errors, sufficient?

Questions for Committee, continued

- What other regulatory changes do you think will minimize errors in the pediatric population?
- This product will be presented to the PAC in 3 to 4 years when studies in the youngest patients are completed. Do you recommend that an earlier safety review of medication errors with Ofirmev™ be presented to a future Pediatric Advisory Committee?

ACKNOWLEDGEMENTS

Division
Ellen Fields, MD, MPH
Judy Racoosin, MD, MPH

PMHS
Elizabeth Durmowicz, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD
Lynne Yao, MD

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Scott Dallas, RPh
Carol Holquist, RPh
Sue Liu, PharmD, ISMP Fellow
Lubna Merchant, MS, PharmD
Kellie Taylor, PharmD, MPH

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Ethan D. Hausman, MD
Hina Mehta, PharmD
Bindi Nikhar, MD
Tracy Pham, PharmD
Alister A. Rubenstein, PharmD, MPH
Judy Staffa, PhD, RPh

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