One Year Post Exclusivity Adverse Event Review: Fluconazole

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Background Drug Information

- **Drug:** Diflucan® (fluconazole)
- **Therapeutic Category:** Antifungal
- **Mechanism of action**: Inhibits arm of fungal C450 pathway
- **Sponsor:** Pfizer
- **Original Market Approval:** January 28, 1990
- **Pediatric Exclusivity Granted:** January 21, 2004 for studies of tinea capitis

Background Drug Information

- **Indication:** Adults and children > 6 months
  - Vaginal, oropharyngeal and esophageal candidiasis
  - Cryptococcal meningitis
  - Infection due to *Candida* (urinary tract infection, peritonitis, systemic)
  - To decrease incidence of candidiasis s/p bone-marrow transplant
- **Dosage:** 3-12 mg/kg/day depending on severity and location of infection (q 3 days preterm neonates)

Pediatric Exclusivity Studies: Safety

- Two efficacy and safety superiority studies
  - Fluconazole (6 mg/kg/day) vs. griseofulvin (11 mg/kg/day) in treatment of tinea capitis for 3 & 6 weeks
  - Children ages 3-12 years
  - Patients enrolled = 880. Fluconazole 6 wks = 286; Fluconazole 3 wks = 302; Griseofulvin 6 wks= 292
  - Efficacy not established: no labeling change
- Animal study to evaluate QTc
  - Beagles (14 days on fluconazole)
  - QTc interval increased: reaffirmed class labeling

Existing Safety Labeling Relevant to Reported Adverse Events

- Warning
  - Bolded: serious hepatic toxicity, including fatality
  - Hypersensitivity (rash)
- Precautions
  - Class effect: prolongation of QT interval
  - Weigh benefit and risk from single oral dose therapy for vaginal yeast infections
  - Multiple significant drug interactions
- Pregnancy Category C: If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

Fluconazole Outpatient Drug Use

- Over 11 million outpatient prescriptions for oral fluconazole products are dispensed annually
  - Approximately 95 % of these are in adults.[1]
  - Approximately 3 % of these are the oral suspension.[2]
- Oral suspension
  - Infants 1 to 2 years of age accounted annually for almost 72 % of all outpatient oral suspension prescriptions (over 300,000).[2,3*]
  - Pediatricians and family practitioners were top prescribers (> 70 %).[2]

[1]Verispan Vector One™: National, MAT April 2002 - March 2005, data extracted 9-21-200
[2]IMS Health, National Prescription Audit *Plus*™, Feb 2002 - Jan 2005, Data Extracted Mar 2005
[3]Caremark Dimension Rx™, Jan 2002- Dec 2004, Data Extracted Mar 2005
*Calculation based on application of proportions of pediatric fluconazole prescriptions in Caremark Dimension RxTM to IMS Health, National Prescription Audit *Plus*™ to estimate number of fluconazole prescriptions dispensed nationwide to pediatric population

Adverse Events (AEs) during the One-Year Post-Exclusivity Period (n=19)

- Total reports during one-year post-exclusivity period (all formulations):
  - 395 reports, all ages*
    - pediatric reports = 29 (19 unduplicated, 8 US)
      - 4 deaths
- Most reports were highly confounded (underlying illness, concomitant medications)
- Although serious adverse events occurred, most were expected or addressed in the labeling.

*includes duplicate reports

Pediatric AEs during the One-Year Post-Exclusivity Period

Fatality (4):

IV and multiple dose therapy

- Coma and multi-organ failure in 7 year old (y.o.) with h/o medulloblastoma, radiation therapy and chemotherapeutic agents*
- 6 week-old with suspected fungal infection, hepatomegaly, elevated liver enzymes and bilirubin, while on fluconazole and cefozopran*; cause of death unspecified

Oral: single dose therapy

- Congenital anomaly (Trisomy 18), stillborn, exposure 6 months prior to pregnancy
- Sudden death (breast milk exposure) in 40 day old infant

*concomitant medications associated with similar toxicity
Labeling for fluconazole includes seizures, hepatic toxicity, and transmission through breast milk

Pediatric AEs during the One-Year Post-Exclusivity Period

Non-fatal AEs (n =15 patients)

- Congenital anomalies (n=3)
- Cardiac events (n=3)
- Metabolic (n =2)
- Hepatic (n= 2)
- Nonfatal fungemia (n=2)
- Dosing errors (n=2)
- Hypersensitivity (n=1)

Pediatric AEs during the One-Year Post-Exclusivity Period Maternal Exposure (n=3)

- Congenital Anomalies
  - Single dose (or short term) treatment
    - Hypospadias and bifid scrotum, exposure 8 weeks prior to pregnancy
    - Syndactyly and finger hypoplasia, exposure 1 week prior to pregnancy
  - Multiple dose treatment
    - Microcephaly, cataract, blindness, small gestation (during first trimester: radiation*, INH*, pyridoxine)

*concomitant medications associated with similar toxicity

Summary: Fluconazole

- Number of pediatric AE reports small compared with adult AE reports, paralleling use
- Most reports confounded
- Although serious AEs occurred, no new unlabeled safety concerns identified
- This completes the one-year post-exclusivity AE reporting as mandated by BPCA.
- FDA recommends routine monitoring of AEs for fluconazole in all populations.
- Does the Advisory Committee concur?

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