

One Year Post Exclusivity Adverse Event Review: emtricitabine

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Background Drug Information

- **Drug:** Emtriva® (emtricitabine)
- **Therapeutic Category:** synthetic nucleoside analog
- **Sponsor:** Gilead
- **Original Market Approval:** July 2, 2003 (capsule) and Sep 28, 2005 (oral solution)
- **Combinations:**
 - Truvada (emtricitabine/tenofovir) approved August 2, 2004 and
 - Atripla (emtricitabine/tenofovir/efavirenz) approved July 12, 2006
- **Pediatric Exclusivity Granted:** May 24, 2006

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Background Drug Information

- **Indication:**
 - Treatment of HIV infection in combination with other antiretroviral agents
- **Daily Oral Dosage:**
 - Adults: 200 mg (capsules) or 240 mg (oral solution)
 - Pediatric patients:
 - 3 mo to 17 years:
 - > 33 kg: 200 mg
 - < 33 kg or cannot swallow capsule: 6 mg/kg (max 240 mg)
 - 0 to 3 mo: 3 mg/kg

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Drug Use Trends: emtricitabine

- Total number of retail prescriptions dispensed for nucleoside reverse transcriptase inhibitors (NRTIs) increased 4% (2.9 to 3.1 million, June 2005 to May 2006 and June 2006 to May 2007)¹
- Prescriptions for emtricitabine (June 2006 to May 2007)¹
 - as a single agent: 1.2% of NRTIs
 - as a part of a combination product: > 25%
- Trends pre- and post-exclusivity period (including combinations)
 - Total outpatient dispensed prescriptions increased 58% (from 673,200 to 1,065,300)¹
 - Total inpatient discharges billed for emtricitabine products increased 34% (from ~7,100 to 9,500)²

¹Verispan, LLC, Vector One® National (VONA), Data extracted July 2007

²RxMarket Advisor™, data extracted July 2007

Drug Use Trends: emtricitabine

- Pediatric patients comprise small portion (<1.5%) of outpatient prescriptions^{1,2} for both single and combination products
- Most common prescribing specialty: Infectious disease (33%) and internal medicine (27%)¹

¹Verispan, LLC, Vector One® National (VONA), Data extracted July 2007

²Verispan, LLC: Total Patient Tracker, June 2004 to May 2007, extracted July 2007

http://www.fda.gov/cder/pediatric/Summaryreview.htm

The screenshot shows the FDA website interface. At the top, it says "U.S. Food and Drug Administration" and "CENTER FOR DRUG EVALUATION AND RESEARCH". Below that, there are navigation links like "CDER Home", "About CDER", "Drug Information", "Regulatory Guidance", "CDER Calendar", "Specific Audiences", and "CDER Archives". A search bar is present with a "GO" button and "powered by Google". The main content area displays "Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies as of October 1, 2007" and "Total Number of Drugs with Summaries Posted: 86". Below this is a table with three columns: "Drug", "Sponsor", and "Review Summary". The table lists three drugs: Dorzolamide - Trusopt (Merck), Emtricitabine - Emtriva (Gilead Sciences), and Ertapenem - Invanz (Merck). An arrow points to the Emtricitabine - Emtriva row. The "Review Summary" column for Emtricitabine - Emtriva contains two links: "Medical" and "Clinical Pharmacology".

Drug	Sponsor	Review Summary
Dorzolamide - Trusopt	Merck	Medical None*
Emtricitabine - Emtriva	Gilead Sciences	Medical Medical Clinical Pharmacology
Ertapenem - Invanz	Merck	Medical Clinical Pharmacology

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Pediatric Exclusivity Studies: emtricitabine

- Pharmacokinetic (pk), safety, efficacy and antiviral activity in pediatric patients with HIV infection > 3 months
- Pk and safety data in HIV-1 exposed neonates
- Data submitted in two stages:
 - March 2005 (3 months and older)
 - March 2006 (neonates)

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Pediatric Exclusivity Study: PK children

- Single dose- escalation study
 - HIV-infected children, n=77 ages 3 months to 17 years (divided into 4 age groups)
 - Exposures from either formulation 6 mg/kg (maximum 240 mg oral solution or 200 mg capsule) similar to exposure estimates reported for adults

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Pediatric Exclusivity Study: Efficacy Children

- Three open, label, non randomized studies in HIV-infected patients, 3 months to 21 y (n=169)
- Treatment naïve or experienced
- Combination therapy: either emtricitabine oral solution or capsules + at least two other antiviral agents
- Efficacy
 - 86 % achieved and sustained HIV RNA < 400 copies/mL and 73% <50 copies/mL
 - Mean increase baseline CD4 count 232 (-945 to 1512) cells/mm³

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Pediatric Exclusivity Study: Safety in Children

AE frequency in children similar to adults except:
Hyperpigmentation: 32% children vs. 13% adults

Common treatment emergent AEs included:

- infections (44%)
- increased cough (28%)
- otitis media (23%)
- vomiting (23%)
- rash (21%)
- diarrhea (20%)
- rhinitis (20%)
- fever (18%)

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Pediatric Exclusivity Study: Neonates

- Open-label non-randomized study in term infants born to HIV-1 infected mothers*, all treated with 6 weeks postnatal ZDV + two 4-day courses of emtricitabine administered during
 - Week 1 and weeks 3 to 6 (n=4)
 - Week 2 and weeks 4 to 7 (n=4)
 - Week 3 and week 5 to 8 (n=4)
 - Week 4 and week 6 to 12 (n=4)

*all mothers received intrapartum IV ZDV or NVP or short course of oral ZDV, +/- antepartum, and postpartum treatment x 6 months

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Pediatric Exclusivity Study: PK Neonates (n=16)

Single dose of 3 mg/kg/day in neonates (36 wk GA and >2.5 kg)

Findings: similar AUC to older children

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Pediatric Exclusivity Study: Safety in Neonates

- No deaths
- SAEs (n=3)
 - Grade 3 necrotizing enterocolitis (NEC) and anemia prior to receiving study drug
 - Grade 3 gastroenteritis and bronchopneumonia, day 106, resolved
 - Grade 4 bronchiolitis, day 43, resolved
- Discontinuations due to AEs:
 - fever most common
 - Grade 3 NEC and anemia withdrawn prior to receiving study drug

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Pediatric Exclusivity Study: Labeling Changes

Clinical Pharmacology: Pediatrics

- Pk findings described, 6 mg/kg/day equivalent to adult dose (Sept 2006)
- Similar AUC in neonates receiving 3 mg/kg/day and older children (Dec 2006)

Precautions: Pediatric Use:

- safety and effectiveness (S & E) in pediatric patients 3 months and older supported by data from 3 open-label, nonrandomized clinical studies (Sept 2006).
- S & E not established < 3 months (Dec 2006)
- Clinical trial described, adverse profile similar with exception of greater frequency of hyperpigmentation (Sept 2006)
- Neonatal AEs described (May 2006)

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Pediatric Exclusivity Study: Labeling Changes

Adverse Reactions

Profile based on 169 HIV-infected pediatric patients treated x 48 weeks (Sept 2006)

- Treatment-emergent AES: infection (44%), hyperpigmentation (32%), increased cough (28%), vomiting (23%), otitis media (23%), rash (21%), rhinitis (20%), diarrhea (20%), fever (18%), pneumonia (15%), gastroenteritis (11%), abdominal pain (10%) & anemia (7%)
- Grade 3 and 4 laboratory abnormalities (9%): amylase > 2x ULN (n=4), neutropenia (<750/mm³, n=3), ALT > 5x ULN (n=2), elevated CPK >4x ULN (n=2)

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Pediatric Exclusivity Study: Labeling Changes

Dosage and Administration:

Dosing added for children:

- 3 months to 17 years (Sept 2006)
- 0 to 3 months (Dec 2006)

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Additional Relevant Safety Labeling

- **Boxed Warning:**
 - lactic acidosis and severe hepatomegaly with steatosis, including fatality with nucleoside analogs
 - Not indicated for chronic HBV
- **Contraindications:** hypersensitivity
- **Warnings:**
 - Lactic Acidosis/Severe hepatomegaly with steatosis
 - Patients co-infected with HIV and HBV: test before initiation of therapy, monitor hepatic function
- **Precautions**
 - Impaired renal function: reduce dosage
 - Drug interactions: none significant for those studied
 - Fat Redistribution
 - Immune Reconstitution Syndrome (inflammatory response to indolent or residual opportunistic infections)

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Additional Relevant Safety Labeling

- Pregnancy Category B
 - Antiretroviral Pregnancy Registry
- Nursing Mothers: CDC recommends not to BF

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Adverse Event Reports and Duplicates: HIV drugs

- Most patients receive multiple drug therapies
- Combination therapies are often initiated and terminated simultaneously
- Each company must submit a report upon notification of an AE with their product
- Direct reports may be received (e.g., from health care professionals, consumers and lawyers)
- Thus, many reports are duplicates

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Adverse Event Reports Since Market Approval: emtricitabine

Raw counts*	All reports (US)	Serious (US)**	Death (US)
All ages	947 (523)	899 (477)	108 (58)
Adults (≥ 17)	774 (403)	745 (376)	92 (49)
Pediatrics (0-16)	35 (27)	35 (27)	6 (5)
Unknown Age	138 (93)	119 (74)	10 (4)

* includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

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Adverse Event Reports during One-Year Post Exclusivity Period: emtricitabine

Raw counts* (*includes duplicates)	All reports (US)	Serious (US)	Death (US)
All ages	497 (261)	478 (243)	45 (30)
Adults (≥ 17)	400 (197)	390 (188)	45 (30)
Pediatrics (0-16)	20 (15)	20 (15)	5 (3)
Unknown Age	77 (49)	68 (40)	56 (38)

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Pediatric Adverse Events One-Year Post Exclusivity (n=15)

Congenital (n=11, 4 fatalities)

- 32 weeks with multiple congenital anomalies
- 23 week twin with cerebral hemorrhage and patent ductus arteriosus
- 32 week stillborn with massive intracranial & brainstem hemorrhage
- 24 day old male twin died from febrile gastroenteritis, dyspnea and malnutrition

No pattern observed, exposure to multiple antiretroviral agents and at various gestational ages

Annual reports from Antiviral Pregnancy Registry (established 1989) for emtricitabine not remarkable

Labeling: Emtricitabine & emtricitabine/tenofovir: Pregnancy Category B
Emtricitabine/tenofovir/efavirenz: Pregnancy Category D (efavirenz may cause fetal harm)

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Pediatric Adverse Events One-Year Post Exclusivity (n=15)

Hepatic (n=3)

16 y/o M with HIV and HCV changed antiviral therapy from stavudine/lamivudine and lopinavir/ritonavir to emtricitabine/tenofovir, lopinavir/ritonavir and tipranavir developed hepatitis and jaundice after 19 days, resolved after discontinuation

16 y/o F with HIV on emtricitabine and didanosine x 1 year added atazanavir and ritonavir. 6 days later, asymptomatic elevations bilirubin (total and indirect) occurred

Labeling:

emtricitabine: pediatric adverse reactions- elevated ALT & GGT
tipranavir: boxed warning for hepatotoxicity
atazanavir: precautions- asymptomatic elevation of bilirubin

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Pediatric Adverse Events One-Year Post Exclusivity (n=15)

Hepatic (continued)

14 mo old male with HIV & congenital toxoplasmosis, receiving combination therapy with emtricitabine, efavirenz and didanosine developed elevated LFTs following accidental overdose (3x emtricitabine), levels declined after discontinuation.

Potential confounding factors: hyperalimentation, surgery/anesthesia, possible sepsis, gabapentin

Labeling:

emtricitabine: pediatric adverse reactions- elevated ALT & GGT

No information regarding increased LFTs or GGT in overdose section

efavirenz: postmarketing experience- hepatic enzyme increase

didanosine: warning- hepatic impairment and toxicity

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Pediatric Adverse Events One-Year Post Exclusivity (n=15)

Gastroenteritis (n=1)

6 y/o female with HIV on emtricitabine, stavudine and lopinavir/ritonavir for >1 year, developed vomiting, ear and eye pain, generalized lymphadenopathy and epigastric tenderness, and later profuse diarrhea. Symptoms resolved after discontinuation of medication and hospitalization for suspected meningitis (negative lumbar puncture, CSF and blood culture)

Labeling: Gastroenteritis is listed under Adverse Reactions/Pediatric Patients

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Summary: emtricitabine

- Labeling updated from exclusivity studies
 - S & E in patients 3 months and older, not established < 3 months
 - AEs similar to adults, except hyperpigmentation
 - Dosing provided for children birth to 17 years
- No new pediatric AEs identified during one-year exclusivity period
- The FDA recommends routine monitoring of emtricitabine for AEs in all populations

Does the Advisory Committee concur?

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