

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**PID#:** D050372

**DATE:** October 10, 2006

**TO:** Lisa L. Mathis, M.D., Associate Director  
Pediatric and Maternal Health Staff (PMHS)  
Office of New Drugs (OND), CDER  
and  
M. Dianne Murphy, M.D., Director  
Office of Pediatric Therapeutics (OPT), OC

**FROM:** Melissa M. Truffa, R.Ph., Safety Evaluator  
Division of Drug Risk Evaluation (DDRE)

**THROUGH:** Rosemary Johann-Liang, M.D., Deputy Director  
for Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation

**SUBJECT:** 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
NDA 20-659 and NDA 20-945  
Drug: Norvir® (ritonavir)  
Pediatric Exclusivity Approval Date: June 14, 2005

**1. EXECUTIVE SUMMARY**

The Adverse Event Reporting System (AERS) was searched for reports of adverse events (serious and non-serious) associated with the use of ritonavir in adult and pediatric patients. Up to the "data lock" date of July 14, 2006, AERS contains 6511 reports for ritonavir (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 6.4 % of the total (417/6511).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, June 14, 2005 to June 14, 2006 (referred to hereafter as the *pediatric exclusivity period*). AERS was searched using a "cut-off" date of July 14, 2006 to allow time for all reports received by June 14, 2006 to be entered into the database. A total of 984 reports (crude count) were received during the pediatric exclusivity period, including both adult and pediatric reports and reports with no reported age. Sixty-eight (crude count) of the 984 reports received during the pediatric exclusivity period reported events in pediatric patient (ages 0-16 years).

After merging duplicate reports and excluding one report because the patient was not receiving ritonavir at the time of the event there were **50** unique pediatric reports received by FDA during the pediatric exclusivity period. These 50 reports represent **33** pediatric reports in patients receiving ritonavir for the treatment of HIV and an additional **17** reports in infants following transplacental exposure to ritonavir.

This review will focus on the **33** pediatric reports in patients receiving ritonavir for the treatment of HIV; the **17** reports in infants following transplacental exposure to ritonavir are summarized in Appendix A and will not be discussed further. Sponsors of all antiretroviral agents including ritonavir participate in an active antiretroviral pregnancy registry<sup>1</sup> to monitor maternal-fetal outcomes of pregnant women exposed to antiretrovirals; ritonavir-specific serious adverse events from maternal-fetal exposures have not been noteworthy in their annual reports.

All serious events (hepatotoxicity-7, Cushing syndrome-5, pancreatitis-2, GI symptoms-2, and skin reactions-3) reported more than once in pediatric patients receiving ritonavir during the pediatric exclusivity period are labeled events. There were three pediatric deaths. None of the reported fatalities were considered directly related to the use of ritonavir but are most likely attributable to underlying conditions (i.e. HIV).

One case of each of following was also reported during the exclusivity period: alopecia, anemia, pseudomonas aeruginosa sepsis, nystagmus with photophobia and strabismus, epistaxis, spontaneous abortion, arthropathy, and convulsion associated with pyrexia. The majority of these events are listed in the ritonavir product labeling. Alopecia, nystagmus, strabismus and spontaneous abortion are unlabeled events.

This review does not reveal any new safety concerns for the use of ritonavir in pediatric patients, and the pediatric adverse event profile observed during the one-year-post exclusivity period is similar to that for adult patients. We will continue routine monitoring of adverse events with the use of ritonavir in pediatric patients.

## **2. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, and PEDIATRIC FILING HISTORY**

### **2.1 Norvir® Product Formulations**

1. Norvir® (ritonavir) 100mg Oral Capsules approved March 1, 1996
2. Norvir® (ritonavir) 80mg/mL Oral Solution originally approved March 1, 1996; reformulated under new NDA approved June 29, 1999.

**2.2 Indication:** Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV infection in patient > 1 month of age.

### **2.3 Pediatric Labeling (approved on October 6, 2005)**

#### **Clinical Pharmacology/Pharmacokinetics/Pediatric Patients**

---

<sup>1</sup> Norvir® (ritonavir) Product Label, Abbott Laboratories, November 2005

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2 to 14 years receiving doses ranging from 250 mg/m<sup>2</sup> twice-daily to 400 mg/m<sup>2</sup> twice-daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m<sup>2</sup> twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m<sup>2</sup>) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg/m<sup>2</sup> twice-daily in pediatric patients > 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m<sup>2</sup>) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m<sup>2</sup> twice-daily in children < 2 years of age. Higher ritonavir exposures were not evident with 450 mg/m<sup>2</sup> twice-daily compared to the 350 mg/m<sup>2</sup> twice-daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice-daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg/m<sup>2</sup> twice-daily in children < 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice-daily.

### Pediatric Use

In HIV-infected patients age > 1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

### Adverse Reactions/Pediatrics:

#### Treatment-Emergent Adverse Events

NORVIR has been studied in 265 pediatric patients > 1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in ≥ 2% of pediatric patients enrolled in NORVIR clinical trials.

#### Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in > 3% of pediatric patients who received treatment with NORVIR either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anemia (4%), and elevated AST (3%).

### Dosage and Administration/Pediatric Patients

Ritonavir should be used in combination with other antiretroviral agents (see General Dosing Guidelines). The recommended dosage of ritonavir in children > 1 month is 350 to 400 mg/m<sup>2</sup> twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m<sup>2</sup> and increased at 2 to 3 day intervals by 50 mg/m<sup>2</sup> twice daily. If patients do not tolerate 400 mg/m<sup>2</sup> twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents, however, alternative therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.

#### Pediatric Dosage Guidelines

Body Surface Area* (m <sup>2</sup> )	Twice Daily Dose 250 mg/m <sup>2</sup>	Twice Daily Dose 300 mg/m <sup>2</sup>	Twice Daily Dose 350 mg/m <sup>2</sup>	Twice Daily Dose 400 mg/m <sup>2</sup>
0.20	0.6 mL (50 mg)	0.75 mL (60 mg)	0.9 mL (70 mg)	1.0 mL (80 mg)
0.25	0.8 mL (62.5 mg)	0.9 mL (75 mg)	1.1 mL (87.5 mg)	1.25 mL (100 mg)
0.50	1.6 mL (125 mg)	1.9 mL (150 mg)	2.2 mL (175 mg)	2.5 mL (200 mg)
0.75	2.3 mL (187.5 mg)	2.8 mL (225 mg)	3.3 mL (262.5 mg)	3.75 mL (300 mg)
1.00	3.1 mL (250 mg)	3.75 mL (300 mg)	4.4 mL (350 mg)	5 mL (400 mg)
1.25	3.9 mL (312.5 mg)	4.7 mL (375 mg)	5.5 mL (437.5 mg)	6.25 mL (500 mg)
1.50	4.7 mL (375 mg)	5.6 mL (450 mg)	6.6 mL (525 mg)	7.5 mL (600 mg)

\* Body surface area can be calculated with the following equation:  $BSA (m^2) = \frac{Ht (Cm) \times Wt (kg)}{7200}$

## 2.4 Pediatric Filing History

Norvir® (ritonavir) is a protease inhibitor indicated in combination with other antiretroviral agents for the treatment of the human immunodeficiency virus (HIV) infection. There are two available formulations 1) 100mg soft gelatin capsules and 2) 80mg/ml oral solution.

The original Pediatric Written Request was issued on April 16, 1999 and was last amended on November 4, 2004. Data from two clinical trials (PACTG 345 and PACTG 366) conducted by the Pediatric AIDS Clinical Trial Group (PACTG) were submitted in response to the Pediatric Written Request and provide for the use of Norvir® (ritonavir) oral solution in pediatric patients from one month to two years of age. Study PACTG 345 is the pivotal study to support use in patient > 1 month to 2 years of age and Study PACTG 366 provided supportive pharmacokinetic and safety data. The Norvir® label was updated with the October 6, 2005 approval of the pediatric efficacy supplements to reflect the new dosing recommendations in pediatric patients (see Section 2.3 above).

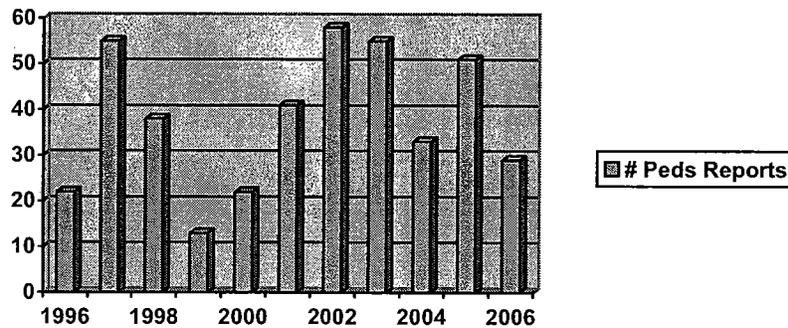
## 3. AERS SEARCH RESULTS: NORVIR® (ritonavir)

### 3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude Counts <sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date through July 14, 2006 (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	5055 (2149)	4726 (1931)	562 (153)
Pediatrics (0-16 yrs.)	417 (205)	380 (185)	39 (23)
Age unknown (Null values)	1039 (649)	920 (564)	102 (34)
Total	6511 (3003)	6026 (2680)	703 (210)

<sup>1</sup> May include duplicates  
<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and medically significant.

**Figure 1: Reporting Trend for Pediatric Reports for Ritonavir (From approval date through July 14, 2006)**



**3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)**

<b>Table 2: Crude counts<sup>1</sup> of AERS Reports for All Sources from Date Pediatric Exclusivity Was Granted June 14, 2005 through July 14, 2006 (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	780 (238)	766 (225)	148 (53)
Pediatrics (0-16 yrs)	68 (39)	63(37)	5 (3)
Age unknown (Null Values)	136( 58)	124 (47)	30 (13)
Total	984 (335)	953 (309)	183 (69)

<sup>1</sup>May include duplicates  
<sup>2</sup>Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and medically significant.

**4. POSTMARKETING REVIEW OF ALL PEDIATRIC ADVERSE EVENTS RECEIVED DURING THE ONE-YEAR AFTER PEDIATRIC MARKETING EXCLUSIVITY**

**4.1 Case Characteristics of Pediatric Cases Received During Pediatric Exclusivity Period (n=33)**

*Note: Four of the reports in this case series involve the use of Kaletra® (lopinavir 200mg/ritonavir 50mg).*

<b>Table 3: Characteristics of Pediatric Cases Reported During Pediatric Exclusivity Period, June 14, 2005 through July 14, 2006 (n=33)</b>		
Gender [n= 32]	Male:	15
	Female:	17
Age [n= 33]	Mean= 9.9 years	
	Median = 11 years; (Range, 1-16 years)	
	0- <1 month =	0
	1 month <2 yrs =	2
	2-5 yrs =	5
	6-11 yrs =	15
	12-16 yrs =	11
Origin [n= 33]	US=	13
	Foreign=	20
Indications [n= 33]	HIV	33
Outcomes [n= 28]	Death-3, Life-Threatening-4, Hospitalization-9, Medically Significant/Other-12	

**4.2 Fatalities (n= 3)**

There were 3 reports of death in pediatric patients during the pediatric exclusivity period. Two are with the use of Kaletra® (lopinavir/ritonavir) and one with the use of atazanavir and ritonavir as part of a combination antiretroviral regimen. None of the reported

fatalities were considered directly related to the use of ritonavir but are most likely attributable to underlying conditions (i.e. HIV). The 3 cases are described below:

**IRS# 5879904, Romania:** A 16-year-old female patient receiving antiretroviral therapy with Kaletra (lopinavir/ritonavir), stavudine, and lamivudine died of cryptococcal meningitis. The patient had two previous episodes of cryptococcal meningitis in the previous year and was on fluconazole for approximately a year for chronic cryptococcal infections.

**ISR# 4897942, South Africa:** Literature report of opsoclonus-myoclonus in 21-month old HIV infected child on antiretroviral therapy (lopinavir/ritonavir, lamivudine, stavudine) as a possible immune reconstitution inflammatory syndrome.<sup>2</sup> The patient died of cardio-respiratory complications secondary to disseminated cytomegalovirus infection.

**IRS# 4865099, South Africa:** A 2-year-old black male patient died due to hemorrhagic pneumonia, ruptured porencephalic cyst, medication error, bronchospasm and deterioration of renal function while enrolled in a Non-BMS clinical trial of atazanavir, stavudine, lamivudine and ritonavir therapies. On 26-Apr-2005, the patient was enrolled in a study which consisted of daily oral therapy with atazanavir 150 mL and ritonavir 0.65 mL initiated for the treatment of HIV infection. On \_\_\_\_\_ the patient presented to the hospital with a history of epileptic seizure for one hour, and a one day history of coughing, vomiting and fever. Therapy with sodium valporate was withheld at admission due to a serum drug level being elevated to 773 mcmol/l (normal range 350-700). At admission, the patient was post-ictal, afebrile with increased urea and creatinine levels, decreased carbon dioxide levels with tachycardia, tachypnea, and harsh breath sounds. Laboratory tests revealed increased urea and creatinine. Therapy with cefotaxime was initiated. From 04-to 05-Aug-2005, the patient experienced medication error. The patient's mother accidentally administered stavudine, lamivudine and ritonavir twice daily instead of once daily. On the morning of 04-Aug-2005, the patient was stable. A cerebral spinal fluid sample was analyzed on 04-Aug-2005 and revealed a very high neutrophil count of 51.8% (normal range 2-5.5), without bacterial or bacterial growth present. By the morning of 05-Aug-2005, the patient's temperature spiked up to 39 degrees C. A serum drug level of sodium valporate had decreased. On \_\_\_\_\_ increased respiratory distress was noted. Oxygen saturation was 74% while on a nasal cannula, the patient was put in an "oxygen box," was suctioned, and given nebulizer treatment. One hour later, the patient was noted to not be breathing and was certified as dead. The cause of death was considered pneumonia and deteriorating renal function. A post-mortem revealed that the right and left lung showed identical features on external examination and on dissection. There was evidence of diffuse, bilateral consolidation and macroscopically the features were those of hemorrhagic bronchopneumonia. There was evidence of intra-alveolar hemorrhage, edema, as well as acute inflammation.

#### **4.3 Summary of Non-Fatal Cases Received During the 1-year Post-Pediatric Exclusivity Period by Primary Adverse Event Described in Narrative (n=30)**

##### ***Hepatic Events (n=7)***

A report from the scientific literature<sup>3</sup> described a patient who developed hepatitis C virus (HCV) while receiving therapy with ritonavir, stavudine, and lamivudine. Another report describes non-alcoholic hepatitis steatosis, increased liver enzymes, increased bilirubin, and hyperglycemia in an obese 14-year-old receiving atazanavir, ritonavir, emtricitabine, and didanosine. Five additional reports describe increased liver enzymes (AST, ALT, GGT) and/or hyperbilirubinemia. Atazanavir was one of the concomitant

<sup>2</sup> Van Toorn R et al. Opsoclonus-myoclonus in an HIV-infected Child on Antiretroviral therapy-Possible Immune Reconstitution Inflammatory Syndrome. Eur J Paed Neurol. 2005; 9:423-426.

<sup>3</sup> Canobio S. et al. Differing Patterns of Liver Disease Progression and Hepatitis C Virus (HCV) Quasispecies Evolution in Children Vertically Co-infected with HCV and Human Immunodeficiency Virus Type 1. J Clin Microbiol. 2004 Sept; 42(9): 4365-69.

antiretrovirals in four of these reports and nevirapine in the fifth. Atazanavir was been associated with asymptomatic hyperbilirubinemia in clinical trials and hepatotoxicity is a labeled event for ritonavir (**Warning**), atazanavir (**Precaution**), and nevirapine (**Boxed Warning**). None of these patients developed liver failure. The following is a case example of increased liver enzymes in a 2-year-old patient.

**ISR#5040465, MFR#ZA-Bristol-Myers-SquibbCompany-13424817, South Africa:** A clinical investigator reported via the National Institute of allergy and Infectious Disease (2006-0511) that a 2-year-old male patient enrolled in a non-BMS trial of atazanavir, stavudine, ritonavir and lamivudine experienced life threatening grade 4 raised aspartate transaminase (AST), alanine transaminase (ALT) and severe gamma glutamyl transferase (GGT). Oral atazanavir 150 mg daily, stavudine 11 mg twice daily, lamivudine 4 ml twice daily and ritonavir 0.5 ml daily therapy were initiated on 11-Aug-2005. Or the patient experienced raised AST and ALT. Laboratory results in showed AST 1343 U/l (N 0-56), ALT 1082 U/l (N 5-30) and GGT 171 U/L (N3-22). The patient was well with no signs of jaundice or liver failure. On 19-Jun-2006, the study medications were interrupted due to the events. On liver function tests showed improvement in the AST and a grade 3 raised GGT.

The ritonavir label states that hepatic transaminases exceeding 5 times the upper level of normal, clinical hepatitis, and jaundice have occurred with the use of ritonavir alone or in combination with other antiretrovirals and there may be increased risk in patients with underlying hepatitis B or C.

***Drug Interaction with fluticasone propionate: Cushing Syndrome (n=5)***

During the exclusivity period five reports of Cushing syndrome were reported with the concomitant use of ritonavir and fluticasone propionate. Four of these reports are derived from two literature reports<sup>4,5</sup>.

**Representative Cases:**

**ISR# 4876536, MFR#FR-GlaxoSmithKline-B0405833A, France:** This case was reported in a literature article and described the occurrence of Cushing Syndrome in a 10-year-old female patient who received fluticasone propionate (Fluticasone) for an unknown drug indication. Concurrent medical conditions included human immunodeficiency virus infection. Co-suspect medication included ritonavir. Concurrent medications included anti-viral medication (HIV treatments (unspecified)). On an unknown date, the patient started ritonavir (dose regimen unknown). On an unknown date after starting ritonavir, the patient started inhaled fluticasone propionate (dose regimen unknown). A few months after starting fluticasone, the patient presented with facial puffiness and asthenia. Proteinuria was negative; cortisol was < 1 µg/dL, ACTH 8 pg/mL. Hydrocortisone was prescribed 10mg/day and gradually increased to 20 mg/day. Face swelling worsened, associated with acne and weight gain (4kg) and high blood pressure (170/90). Adrenal insufficiency diagnosed on cortisol levels and synacthene test. Withdrawal of steroids led to normalization of blood pressure within a week and of facial features within 3-4 months. The author's commented that "Ritonavir is a potent inhibitor of cytochrome P450 3A4 even when used in "low" doses. Fluticasone has an extensive first pass metabolism and liver clearance mediated by cytochrome P450. Due to wide use of Fluticasone and belief of safety of inhaled therapy, such complications may go under diagnosed leading to severe symptoms. Co-administration of Ritonavir / inhaled Fluticasone leads to a high risk of Cushing syndrome and adrenal suppression and should be contraindicated or closely monitored if no other option is available."

<sup>4</sup> Dolfus C et al. Cushing syndrome in 3 children treated with HAART and inhaled fluticasone. 10<sup>th</sup> Eur AIDS Conf (EACS). 2005; 127-128:11

<sup>5</sup> Johnson S et al. Cushing Syndrome with Secondary Adrenal Insufficiency from Concomitnat therapy with Ritonavir and Fluticasone. J Pediatr 2006; 148:386-8

**IRS# 4813571, MFR# US-GlaxoSmithKline-A0547383A, US:** This case described the occurrence of Cushing syndrome in an 11-year-old female patient who received Fluticasone propionate+salmeterol xinafoate 250/50mcg(Advair) multi dose powder inhaler over a period of 1 week for asthma. Concurrent medical conditions included asthma and human immunodeficiency virus. Co-suspect medications included Ritonavir. Concurrent unspecified medications were received. In 2005 the patient started Fluticasone propionate+salmeterol xinafoate (inhaled) at 1 puff twice per day. Approximately 1 week later, the patient experienced Cushing syndrome. Upon follow-up, the reported stated that the patient was admitted to the hospital. Treatment with Advair and ritonavir was discontinued and the patient began treatment with efavirenz (Sustiva), montelukast(Singulair) and (cetirizine)Zyrtec. It was suspected that the patient had allergic related asthma. The reporter considered the events were life threatening and clinically significant (or requiring intervention). The events improved.

The warning section of the Norvir® label was updated on March 28, 2005 to include a statement about the concomitant use of ritonavir and fluticasone propionate. “A drug interaction study in healthy subjects has shown that ritonavir significantly increases the plasma fluticasone propionate exposures, resulting in significantly decreased serum levels of cortisol concentrations. Systemic corticosteroid effects, including Cushing syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, co-administration of fluticasone propionate and NORVIR is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.” DDRE also reviewed this issue in December 2004<sup>6</sup>.

***Pancreatitis (n=2)***

Two pediatric patients experienced pancreatitis with the use of ritonavir in combination with other antiretrovirals. There is a warning in the Norvir® label that pancreatitis has been observed in patients receiving ritonavir.

***Gastrointestinal (GI) symptoms (n=2)***

There are two reports of GI symptoms (including diarrhea, nausea and vomiting) with the use of ritonavir and other antiretrovirals. Gastrointestinal events are labeled events and are not unexpected with the use of ritonavir and other antiretrovirals.

***Skin Reactions (n=3)***

There is one report each for the following: a macular rash that resulted in hospitalization for a toxic skin reaction; a “multiforme-like skin rash” with mild angioedema and a fever; and erythematous rash, fever, eosinophilia and increased liver enzymes. The last patient clinical and biological symptoms resolved after abacavir, efavirenz and Bactrim were discontinued; therapy with fosamprenavir and ritonavir continued. Maculopapular rash and erythema multiforme have been associated with the use of ritonavir and are listed events in ritonavir product labeling.

***Drug Ineffective (n=3)***

---

<sup>6</sup> Memorandum dated December 3, 2004 from Joyce Weaver, PharmD. HPA-axis suppression with fluticasone propionate.

There are 3 literature reports of patients not responding to HAART regimens that include ritonavir<sup>7</sup>.

***Miscellaneous (n=8)***

During the pediatric exclusivity period one case of each of following was reported: alopecia, anemia, pseudomonas aeruginosa sepsis, nystagmus with photophobia and strabismus, epistaxis, spontaneous abortion, arthropathy, and convulsion associated with pyrexia. The majority of these events are listed in the ritonavir product labeling. Alopecia, nystagmus, strabismus and spontaneous abortion are unlabeled events.

**5. SUMMARY/RECOMMENDATIONS**

All serious events (hepatotoxicity, Cushing syndrome, pancreatitis, GI symptoms, and skin reactions) reported more than once in pediatric patients receiving ritonavir during the pediatric exclusivity period are labeled events for ritonavir. There were three pediatric deaths. None of the reported fatalities were considered directly related to the use of ritonavir but are most likely attributable to underlying conditions (i.e. HIV).

During the pediatric exclusivity period one case of each of following was reported: alopecia, anemia, pseudomonas aeruginosa sepsis, nystagmus with photophobia and strabismus, epistaxis, spontaneous abortion, arthropathy, and convulsion associated with pyrexia. The majority of these events are listed in the ritonavir product labeling. Alopecia, nystagmus, strabismus and spontaneous abortion are unlabeled events.

This review does not reveal any new safety concerns for the use of ritonavir in pediatric patients, and the pediatric adverse event profile observed during the one-year-post exclusivity period is similar to that for adult patients. We will continue routine monitoring of adverse events with the use of ritonavir in pediatric patients.

Melissa M. Truffa, R.Ph 10/10/06  
Reviewer's Signature / Date: /s/

Rosemary Johann-Liang, M.D., 10/10//06  
Deputy Division Director Signature / Date: /s/

---

<sup>7</sup> Vigano A et al. Efficacy and Tolerability of Multiple Drug Therapy in HIV-infected children. J Infect 2005; 50(5): 404-11



Appendix A, Table 4—All Maternal to Fetal Exposure Cases with Ritonavir Received During the Pediatric Exclusivity Period (N=17)

Case #	Sex/age/ Location Outcome	Antiretrovirals	Infant's Reported Adverse Event	Comment
1.	M/newborn "Twin A" France Hosp	Mother: ABV/ZDV/3TC until 16 weeks of gestation LPV/RTV/ZDV/3TC after 16 weeks gestation At delivery: zidovudine IV	Fetal growth retardation Oligohydramnios Anemia Necrotizing colitis Large intestine perforation Peritonitis	Twins born at 32 weeks gestation to 35-year-old mother with a history of sickle-cell anemia. C-Section required for fetal growth retardation, premature labor and premature rupture of membranes. Anemia and respiratory distress two hours after birth. Necrotizing colitis was diagnosed 7 days after birth. Patient recovered after treatment, surgery, antibiotics, and blood transfusions.
2.	M/newborn "Twin B" France Hosp	Mother: ABV/ZDV/3TC until 16 weeks of gestation LPV/RTV/ZDV/3TC after 16 weeks gestation At delivery: zidovudine IV	Fetal growth retardation Enteritis	Twins born at 32 weeks gestation to 35-year-old mother with history of sickle-cell anemia. C-Section required for fetal growth retardation, premature labor and premature rupture of membranes. Anemia and respiratory distress after birth. Enteritis 7 days after birth. Patient recovered.
3.	F/newborn GB Congenital anomaly	Mother: LPV/RTV//3TC/ZDV 3 <sup>rd</sup> trimester	Ventricular Septal Defect (VSD)	Delivery at 38 weeks of gestation to 31-year-old black female. Diagnosed with mid-muscular VSD at birth.
4.	M/newborn France Hosp	Mother: SQV/RTV/d4T/ddI started at 26 <sup>th</sup> week of gestation	Hypertriglyceridemia Hypotonia Anemia	Born at 38 weeks of gestation by C-section. Stavudine and didanosine for 6 weeks. During 1 <sup>st</sup> month developed anemia, hypertriglyceridemia during 2 <sup>nd</sup> month and hypotonia during 3 <sup>rd</sup> month.
5.	5762420 M France Hosp	Mother: TDF/LPV/RTV/ddc. At delivery: zidovudine IV	Mental Retardation Developmental delay at 3 yrs of age	Born at 38 weeks of gestation by C-section. Zidovudine for 6 weeks. At 3 years of age developed medically important mental retardation and developmental delay.
6.	5938229 M/newborn US Congenital Anomaly	Mother: TMC114/RTV/TDF/ZDV	Micrognathia Cardiac murmur	Phase 2 Study for TMC114/ritonavir in HIV experienced patients. Born at 38 weeks of gestation by C-section with congenital anomaly of micrognathia. Oral zidovudine was started after birth. Erythema toxicum diagnosed 10 days after birth.
7.	5942223 M/newborn/ PR Death	Mother: SQV/RTV/ZDV/3TC from 17.4 weeks gestation	Intra-uterine death Umbilical cord around neck	Mother is a 35-year-old Hispanic female with severe endometriosis. At 34 weeks gestation she delivered following intrauterine death. Nuchal cord was noted. No birth defects were noted.

Table 4—All Maternal to Fetal Exposure Cases with Ritonavir Received During the Pediatric Exclusivity Period (N=17)

Case #	Sex/age/ Location Outcome	Antiretrovirals	Infant's Reported Adverse Event	Comment
8.	M/newborn/ US Congenital anomaly	Mother: ATV/RTV from 5 to 27 weeks gestation TDF/FTC from 5 week until delivery. LPV/RTV from 27 week until delivery	Falot's Tetralogy DiGeorge syndrome Cleft palate Pulmonary artery atresia Bilateral small kidneys Nephrocalcinosis Hypospadias	28-year-old Caucasian female delivered at 34 weeks gestation. Multiple congenital anomalies. An ultrasound the month before revealed Falot's tetralogy.
9.	M/newborn Netherlands Congenital anomaly	Mother: LPV/RTV/ZDV/3TC started in 3 <sup>rd</sup> trimester	Hypospadias	Born at 39 weeks to 27-year-old black female. Hypospadias noted at birth.
10.	F/newborn Netherlands Congenital Anomaly	Mother: LPV/RTV/TDF/ZDV/3TC throughout pregnancy	Congenital pyelocaliectasis	Born at 36 weeks to a 27-year-old black female. Dilated right pyelum noted at birth.
11.	F/newborn US Congenital Anomaly	Mother: TDF/FTC/AZV/RTV/NFV ZDV/3TC throughout pregnancy	Polydactyly	Born at 34 weeks gestation to 39-year-old female. Polydactyly noted at birth.
12.	F/newborn US Hosp	AZV/RTV/ZDV/3TC/ddI/TDF throughout pregnancy	Intra-uterine growth retardation Bradycardia at delivery	Born at 36 weeks of gestation to 25-year-old mother. C-section due to intra-uterine growth retardation and bradycardia.
13.	M/newborn France Hosp	Mother: ddI/IDV/RTV/ABV from 23 weeks gestation NVP x 1 dose at delivery	Neutropenia Anemia Lactic acid increased Hypertriglyceridemia Mycrocytosis	Born at 38 weeks of gestation by C-section. Didanosine syrup for 6 weeks and one oral dose of nevirapine day 2 after birth. Possible Thalassemia. At 24 months developmental speech disorder still present at 4 years of age.
14.	M/newborn France Hosp	Mother: d4T/ 3TC/RTV/SQV from week 2 of gestation At delivery: zidovudine IV	Neutropenia, blood lactate increased, hypertriglyceridemia, increased pyruvate, hemangioma, CPK increased, failure to thrive	Born at 38 weeks of gestation by C-Section. Infant received 7 weeks of therapy with stavudine.

Table 4—All Maternal to Fetal Exposure Cases with Ritonavir Received During the Pediatric Exclusivity Period (N=17)

Case #	Sex/age/ Location Outcome	Antiretrovirals	Infant's Reported Adverse Event	Comment
15. 5799645 5816272	F/newborn France Hosp	Mother: ATV/RTV/ddI/ 3TC/TDF throughout pregnancy At delivery: zidovudine IV	Enterocolitis hemorrhagic Hypoglycemia Jaundice	Born at 33.5 weeks gestation by C-section to 35-year-old female experiencing pancreatitis. Patient received oral zidovudine for 3-4 weeks.
16. 6063491	Unk/newborn US Congenital anomaly	Mother: ATZ/RTV/TDF/FTC prior to conception and for 8 weeks then switched to LPV/RTV/ABC/3TC/ZDV x 8 weeks during pregnancy then switched to NFV/3TC/ZDV x 20 weeks until delivery	Trisomy 15 Seizure	Born at 36 weeks gestation to 30-year-old female. Partial Trisomy 15 and seizure disorder were noted at birth.
17. 5751345 5752878 5876762	F/3 months France Hosp	At delivery: zidovudine IV Mother: APV/RTV/TDF/3TC throughout pregnancy At delivery: zidovudine IV	Nystagmus, eye movement disorder, lacrimation increased, CPK increased, lactic acid increased	Born at 40 weeks gestation by vaginal delivery. Oral lamivudine for 1 month after birth. Two months later at age 3 months patient was hospitalized for nystagmus, abnormal eye movement and lacrimation.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Melissa Truffa  
10/10/2006 11:50:21 AM  
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang  
10/10/2006 02:35:37 PM  
MEDICAL OFFICER