U.S. FOOD & DRUG ADMINISTRATION

HIV Email Updates

from the FDA Office of Health and Constituent Affairs

FDA HIV Email Updates provide information about FDA HIV product approval, safety warnings, medical product labeling changes, notices of upcoming meetings, and notices about proposed regulatory guidances.

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Today FDA approved updates to the Isentress (raltegravir) label to expand the patient population to include HIV-1 exposed full term neonates (birth to 4 weeks of age and weighing at least 2 kg). The following information was added to the package insert.

Section 1: INDICATIONS AND USAGE

- **Pediatric Patients:** ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 2 kg.

Section 2: DOSAGE AND ADMINISTRATION

- Recommended Dose for ISENTRESS For Oral Suspension in Full-Term Neonates (Birth to 4 Weeks [28 days] of Age)
- **Note:** If the mother has taken ISENTRESS or ISENTRESS HD 2-24 hours before delivery, the neonate's first dose should be given between 24-48 hours after birth.

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing †	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily
*The dosing recommendations are based on approximately 1.5 mg/kg/dose. †The dosing recommendations are based on approximately 3 mg/kg/dose.	

Section 6: ADVERSE REACTIONS

- **HIV-1 Exposed Neonates:** Forty-two neonates were treated with ISENTRESS for up to 6 weeks from birth, and followed for a total of 24 weeks in IMPAACT P1110 [see Use in Specific Populations (8.4)]. There were no drug related clinical adverse reactions and three drug-related laboratory adverse reactions (one case of transient Grade 4 neutropenia in a subject receiving zidovudine-containing regimen for prevention of mother to child transmission (PMTCT), and two bilirubin elevations (one each, Grade 1 and Grade 2) considered non-serious and not requiring specific therapy). The safety profile in neonates was generally similar to that observed in older patients treated with ISENTRESS. No clinically meaningful differences in the adverse event profile of neonates were observed when compared to adults.

Section 8: USE IN SPECIFIC POPULATIONS

- **8.4 Pediatric Use**

  HIV-1 Exposed Neonates: The safety and pharmacokinetics of ISENTRESS for oral suspension were evaluated in 42 full-term HIV-1 exposed neonates at high risk of acquiring HIV-1 infection in a Phase 1, open-label, multicenter clinical study, IMPAACT P1110. Cohort 1 neonates received 2 single doses of ISENTRESS for oral suspension: the first within 48 hours of birth and the second at 7 to 10 days of age. Cohort 2 neonates received daily dosing of ISENTRESS for oral suspension for 6 weeks: 1.5 mg/kg once daily starting within 48 hours of birth through Day 7 (week 1); 3 mg/kg twice daily on Days 8 to 28 of age (weeks 2 to 4); and 6 mg/kg twice daily on Days 29 to 42 of age (weeks 5 and 6). Sixteen neonates were enrolled in Cohort 1 (10 were exposed and 6 were unexposed to raltegravir in utero) and 26 in Cohort 2 (all unexposed to raltegravir in utero); all infants received a standard of care antiretroviral drug regimen for prevention of mother to child transmission. All enrolled neonates were followed for safety for a duration of 24 weeks. The 42 infants were 52% male, 69% Black and 12% Caucasian. HIV-1 status was assessed by nucleic acid test at birth, week 6 and week 24; all patients were HIV-1 negative at completion of the study. The safety profile was comparable to that observed in adults [see Adverse Reactions (6.1)].

ISENTRESS is not recommended in pre-term neonates or in pediatric patients weighing less than 2 kg.

Section 12:CLINICAL PHARMACOLOGY

- **12.3 Pharmacokinetics**: Elimination of raltegravir *in vivo* in human is primarily through the UGT1A1-mediated glucuronidation pathway. UGT1A1 catalytic activity is negligible at birth and matures after birth. The dose recommended for neonates less than 4 weeks of age takes into consideration the rapidly increasing UGT1A1 activity and drug clearance from birth to 4 weeks of age. Table 15 displays pharmacokinetic parameters for neonates receiving the granules for oral suspension at the recommended dose *[see Dosage and Administration (2.3)].*

Table 15: Raltegravir Pharmacokinetic Parameters from IMPAACT P1110 Following Age and Weight Based Dosing of Oral Suspension

Age (hours/days) at PK Sampling	Dose (See Table 5)	N*	Geometric Mean (%CV†) AUC (μM•hr)	Geometric Mean (%CV†) C_{trough} (nM)
Birth – 48 hours	**1.5 mg/kg once daily**	**25**	**85.9 (38.4%)‡**	**2132.9 (64.2%)‡**
15 to 18 days	**3.0 mg/kg twice daily**	**23**	**32.2 (43.3%)§**	**1255.5 (83.7%)§**

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.
‡ $AUC_{0\text{-}24hr}$ (N = 24) and C_{24hr}
§$AUC_{0\text{-}12hr}$ and C_{12hr}

- **12.5 Pharmacogenomics**

UGT1A1 Polymorphism: There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

In the neonatal study IMPAACT P1110, there was no association between apparent clearance (CL/F) of raltegravir and UGT 1A1 genotype polymorphisms.

The updated label will soon be available at drugs@fda or DailyMed

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