Pediatric Focused Safety Review
Sustiva (efavirenz)
Pediatric Advisory Committee Meeting
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Outline

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Background Information
Sustiva (efavirenz)

- **Drug**: Sustiva (efavirenz)
- **Drug Category**: Antiretroviral Agent (non-nucleoside reverse transcriptase inhibitor)
- **Indications**:
  - In combination with other antiretroviral agents for the treatment of human immunodeficiency virus type I infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kg.
- **Dose**: 600 mg once daily (maximum dose 800 mg daily)
- **Formulation**: 200 mg and 50 mg capsules; 600 mg tablet
- **Sponsor**: Bristol-Myers Squibb Pharma Company

Background Information
Sustiva (efavirenz)

September 17, 1998: Original market approval (3 years and older).

May 2, 2013: Approval in pediatric patients 3 months to 3 years*

- Prompted current safety review.*
- PREA requirements fulfilled for pediatric patients from 3 months and older.
- Waived pediatric study requirement for ages 0 to < 3 months because Sustiva would be ineffective and/or unsafe in this age group.

Relevant Safety Labeling
Sustiva (efavirenz)

Section 4 Contraindications

- Sustiva is contraindicated in patients with previously demonstrated hypersensitivity (e. g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product (4.1)).

Relevant Safety Labeling
Sustiva (efavirenz)

- **Section 5 WARNINGS AND PRECAUTIONS**
  - 5.1 Drug Interactions
  - 5.2 Resistance
  - 5.3 Coadministration with Related Products
  - 5.4 Psychiatric Symptoms
  - 5.5 Nervous Symptoms
  - 5.6 Embryo-Fetal Toxicity
  - 5.7 Rash
  - 5.8 Hepatotoxicity
  - 5.9 Convulsions
  - 5.10 Lipid Elevations
  - 5.11 Immune Reconstitution Syndrome
  - 5.12 Fat Redistribution

Basis of Approval, Patients 3 months to 3 years Sustiva (efavirenz)

- **Matching pharmacokinetics (PK)** in patients 3 months and older to adults
  - Demonstrating antiviral activity and safety

- **Three OL studies** evaluated pharmacokinetics (PK), safety, tolerability, and anti-viral activity of **efavirenz** in combination with …
  - **didanosine** and **emtricitabine** in antiretroviral-naïve and -experienced pediatric patients (3 months up to 6 years of age; n=37)
  - **didanosine** and **emtricitabine** in antiretroviral-naïve pediatric patients (3 months up to 21 years of age; n=43)
  - **nelfinavir** and a **nucleoside reverse transcriptase inhibitor** (NRTI) in antiretroviral-naïve and NRTI-experienced pediatric patients (3 months up to 16 years of age; n=102)

Safety in Three OL Pediatric Studies Sustiva (efavirenz)

- **Adverse reactions (ARs)** observed in these three OL pediatric trials were similar to ARs observed in adult trials except that the incidence of rash was higher in pediatric patients (32% for all grades, regardless of causality) and more often a higher grade than in adults.

  - 2 pediatric patients (1.1%) experienced Grade 3 rash (confluent rash with fever, generalized rash)
  - 4 pediatric patients (2.2%) experienced Grade 4 rash (all erythema multiforme).
  - 5 pediatric patients (2.7%) discontinued from the study because of rash.

Pediatric Labeling Changes
Sustiva (efavirenz)

- **8.4 Pediatric Use**

  The safety, PK profile, and virologic and immunologic responses of Sustiva were evaluated in antiretroviral-naïve and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three OL clinical trials *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*

  Use of Sustiva in patients younger than 3 months of age OR less than 3.5 kg body weight is not recommended because safety, PK, and antiviral activity of Sustiva have not been evaluated in this age group and there is a risk of developing HIV resistance if Sustiva is under dosed. See *Dosage and Administration (2.2) for dosing recommendations for pediatric patients.*

Pediatric Drug Utilization
Efavirenz[1]

Nationally estimated number of patients with dispensed prescriptions for efavirenz-containing products, stratified by age, from U.S. outpatient retail pharmacies, March 2013 through February 2016, aggregated.

	Patient count* (N)	Share (%)
Atripla Total Patients	**145,501**	**100.0%**
0-16 years old	405	0.3%
0-11 months old	17	4.2%
1-16 years old	390	96.3%
17+ years old	145,079	99.7%
Unknown age	864	0.6%
Sustiva Total Patients	**25,079**	**100.0%**
0-16 years old	328	1.3%
0-11 months old	0	—
1-16 years old	328	100.0%
17+ years old	24,733	98.6%
Unknown age	217	0.9%

1 Source: IMS Health, Total Patient Tracker. June 2013 through May 2016. Extracted March 2016.

* Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months old). Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

Adverse Events: Sustiva (efavirenz)

Number of adult and pediatric FDA Adverse Event Reporting System (FAERS) reports received since pediatric labeling

Table 3.2.1 Total Adult and Pediatric FAERS reports* 02-May-2013 to 29-Feb-2016 with Efavirenz

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	1881 (813)	1508 (462)	215 (36)
Pediatrics (0 - <17 years)	145 (35)	**143‡ (34)**	26§ (7)

** May include duplicates and transplacental exposures, and have not been assessed for causality*

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡See Figure 3.2.2

§ Two additional reports of pediatric deaths were identified among reports not reporting an age.

Serious Adverse Events: Sustiva (efavirenz)

Total pediatric reports reviewed with serious outcome (n=143)
Pediatric reports with outcome of death (n=26)

Excluded Reports* (n=116)
(including 17 deaths)
- Duplicates (n=31) (including 7 deaths)
- Transplacental exposure (n=83) (including 10 deaths)
- No individual patient identified (n=2)

Pediatric Case Series (n=27)
(Including 9 deaths)
Age 0 to < 17 years
Fatal: 9 cases
Non-Fatal:18 cases

* DPV reviewed these cases; however, they were excluded from the case series for the reasons listed in the above table.

Adverse Events: Sustiva (efavirenz)
Summary of Pediatric Fatal Cases (n=9)

Immune Reconstitution Inflammatory Syndrome (IRIS) (n=3)

- 14-year old male, HIV infection and pulmonary mycobacterium-avium-intra-cellulare complex (MAI)
- 12-year old male, HIV infection, Kaposi sarcoma, started on tuberculosis therapy
- 8-year old female, HIV infection and pulmonary tuberculosis

Antiretroviral Drug Resistance (n=1)

- 10-year old male, HIV infection treated since ~ 5 years of age

HIV-related opportunistic infection (n=3)

- Two, 16-year old females, and one, 14-year old male.

Unspecified infection (n=2)

- 2-year old female
- 3-month old female

Note: unlabeled events (n=3) will be underlined

Summary of All Non-Fatal Adverse Events (< 17 years)

Labeled Events (n=11)

5 Warnings and Precautions

5.4 Psychiatric Symptoms (n=1)
5.7 Rash (n=2)
5.8 Hepatotoxicity (n=1)
5.11 Immune Reconstitution Syndrome (n=3)

6 Adverse Reactions

Peripheral neuropathy (n=1)
Ataxia (n=2)
Pancreatitis (n=1)

Unlabeled Events (n=3)

Three unlabeled events were identified:

- Catatonia: (n=1) 1 pediatric patient, 16-years of age; 3 adult patients.
- Hypersensitivity: (n=1)*
- Fanconi syndrome acquired: (n=1) *

*potentially confounded

Disease related events (n=4)

Summary: Sustiva (efavirenz)

- This concludes the pediatric focused safety review for Sustiva (efavirenz).
- FDA is considering adding the term catatonia to labeling.
- FDA recommends ongoing routine pharmacovigilance.
- Does the Committee concur?

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