Efavirenz (EFV)

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Formulations

Generic Formulations

- 50-mg and 200-mg capsules
- 600-mg tablet

Fixed-Dose Combination (FDC) Tablets

- Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi and generic] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonatal Dose

- Efavirenz (EFV) is not approved for use in neonates.

Pediatric Dose

- EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

Infants and Children Aged 3 Months to <3 Years and Weighing ≥3.5 kg

- The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) **does not recommend** the use of EFV in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.

Selected Adverse Events

- Rash, which is generally mild and transient
- Central nervous system (CNS) symptoms, such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation, late-onset ataxia, and encephalopathy
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation
- Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests.

Special Instructions

- EFV capsules and tablets can be swallowed whole, or EFV capsules can be administered by sprinkling the contents of an opened capsule on food, as described below.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- Administer EFV and FDC formulations of EFV on an empty stomach. Avoid administration with a high-fat meal because this has the potential to increase absorption.

Children Aged ≥3 Years and Weighing ≥10 kg

Once-Daily Doses of EFV by Weight

Weight	EFV Dose[a,b]
10 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg
20 kg to <25 kg	300 mg
25 kg to <32.5 kg	350 mg
32.5 kg to <40 kg	400 mg
≥40 kg	600 mg

[a] The dose in mg can be dispensed in any combination of capsule strengths. Capsules may be administered by sprinkling the contents onto an age-appropriate food (see Special Instructions below).

[b] Some experts recommend a dose of EFV 367 mg per m^2 of body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see the Pediatric Use section below for details). Weight bands approximate a dose of EFV 367 mg per m^2 of body surface area, with a maximum dose of 600 mg.

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- EFV 600 mg once daily

EFV 600 mg/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

[Symfi] EFV 600 mg/Lamivudine (3TC)/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

EFV 400 mg/3TC/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

Instructions for Using the EFV Capsule as a Sprinkle Preparation With Food

- Hold capsule horizontally over a small container and carefully twist open to avoid spillage.
- Gently mix capsule contents with 1 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt).
- Administer within 30 minutes of mixing, and do not consume additional food for 2 hours after administration.

Metabolism/Elimination

- Cytochrome P450 (CYP) 2B6 is the primary enzyme for EFV metabolism. CYP2A6, CYP3A4, CYP3A5, and uridine diphosphate glucuronosyltransferases (UGT) also contribute to metabolism.
- CYP3A and CYP2B6 inducer *in vivo*
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP, particularly in CYP2B6. Slower metabolizers are at higher risk of toxicity. See the Therapeutic Drug Monitoring section below for information about the management of mild or moderate toxicity.

EFV Dosing in Children With Hepatic Impairment

- EFV **is not recommended** for children with moderate or severe hepatic impairment.

Efavirenz FDC Dosing in Children With Renal Impairment

- Because EFV FDC products contain TDF, lamivudine, and/or emtricitabine that require dose adjustments based on renal function, they should not be used in children with creatinine clearance <50 mL/min or in children on dialysis.

Note: EFV 400 mg/3TC/TDF has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in children in a multiethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥40 kg. Therapeutic drug monitoring is suggested by some Panel members when EFV 400 mg/3TC/TDF is used in children weighing ≥40 kg (see the Therapeutic Drug Monitoring section below).	

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism*: Coadministration of efavirenz (EFV) with drugs that are primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of EFV, resulting in lower plasma concentrations. There is potential for multiple drug interactions with EFV. Importantly, dose adjustment or the addition of ritonavir may be necessary when EFV is used in combination with atazanavir (ATV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).
- Before EFV is administered, a child's medication profile should be reviewed carefully for potential drug interactions with EFV.
- Corrected QT (QTc) prolongation has been observed with the use of EFV.[1,2] An alternative to EFV should be considered in children who are receiving a drug that has a known risk of Torsades de Pointes or in children who are at higher risk of Torsades de Pointes.

Major Toxicities

- *More common:* Skin rash and increased transaminase levels. Central nervous system (CNS) abnormalities—such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, and seizures—have been reported, primarily in adults. See Table 17a. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity for information on managing these toxicities.
- *Rare:* QTc prolongation has been observed with the use of EFV, and Torsades de Pointes has been reported with EFV use.[3] An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance use) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

EFV has been approved by the U.S. Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged ≥3 months and weighing ≥3.5 kg. The FDA also has approved the use of the fixed-dose combination of EFV 400 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥35 kg.

Efficacy in Clinical Trials

EFV-based regimens have proven virologically superior or non-inferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, ATV, elvitegravir, raltegravir, and MVC.[4-10] EFV was shown to be inferior to dolutegravir (DTG) in the SINGLE trial in adults, which compared the virologic response of DTG plus abacavir/3TC with that of EFV/TDF/emtricitabine (FTC) at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the EFV group.[11]

In clinical trials in adults and children with HIV, EFV used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. The 96-week results of the Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy (ENCORE) 1 trial, a randomized trial in adults, showed that EFV 400 mg used in combination with TDF and FTC was non-inferior to EFV 600 mg used in combination with TDF and FTC.[12] EFV used in combination either with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety comparable to what has been seen in adults.[13-15]

Pharmacokinetics: Pharmacogenomics

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of EFV may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for EFV metabolism, and children with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher EFV levels in these children than in those with the G/G or G/T genotypes.[16-19] CYP2B6-516-T/T allele frequency varies by ethnicity. In a study of adults from the United States and Italy, this allele had a frequency of 24.4% among White participants, 31.3% among Black participants, and 34.9% among Hispanic participants.[20] A retrospective study of children in a multiethnic, high-income setting confirmed that EFV plasma concentrations can vary among children. The interindividual variability could be explained in large part by polymorphisms in drug metabolizing genes, as well as by age at treatment initiation and time since treatment initiation.[21] International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1070 has shown that aggressive dosing with approximately 40 mg/kg of EFV using opened capsules resulted in therapeutic EFV concentrations in 58% of children aged <3 years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.[19,22] Optimal dosing may require pre-treatment CYP2B6 genotyping in children aged <3 years (see Pharmacokinetics and Dosing: Infants and Children Aged <3 Years below).[18,19,22]

Other variants—CYP2B6 alleles and variant CYP2A6 alleles—have been found to influence EFV concentrations in adults and children.[18,23-26]

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

The Panel **does not recommend** the use of EFV in children aged 3 months to <3 years. Pharmacokinetic (PK) data in children aged <3 years or weighing <14 kg have shown that it is difficult to achieve target trough concentrations in this age group.[22,27]

Pharmacokinetics: Children Aged ≥3 Years and Adolescents

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, EFV concentrations can be suboptimal.[16,28-32] Therefore, some experts recommend using therapeutic drug monitoring (TDM) in children who are receiving EFV and possibly using higher doses in young children, especially in certain clinical situations, such as virologic rebound or lack of response in an adherent child. In one study in which the EFV dose was adjusted in response to measurement of the area under the curve, the median administered dose was EFV 13 mg/kg (367 mg per m^2 of body surface area), and the range was from 3 mg/kg to 23 mg/kg (69–559 mg per m^2 of body surface area).[33]

Toxicity: Children Versus Adults

The toxicity profile for EFV differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.[34] The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare.

Multiple studies in adults have shown that EFV use is associated with low vitamin D levels, and several studies have found an association between EFV use and low bone mineral density.[35-38] EFV induces CYP3A4 and CYP24 enzymes that may affect vitamin D homeostasis. Because of these findings, the Panel recommends measurement of vitamin D in children receiving EFV and vitamin D supplementation for those with vitamin D deficiency (see Table 17j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis).

In adults, CNS symptoms are commonly reported and affected 29.6% of people in one meta-analysis of randomized trials.[39] These symptoms usually occur early in treatment and rarely require drug discontinuation, but they sometimes can persist for months. Administering EFV at bedtime appears to decrease the occurrence and severity of these neuropsychiatric AEs. For people who can swallow capsules or tablets, ensuring that EFV is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. In several studies, the incidence of neuropsychiatric AEs was correlated with EFV plasma concentrations, and the symptoms occurred more frequently in people with higher concentrations.[40-43] The ENCORE1 study in adults demonstrated that a dose of EFV 400 mg is associated with fewer AEs and a non-inferior virologic response when compared with the recommended 600-mg dose of EFV.[12,44] A Tanzanian study of children aged 6 to 12 years showed that those who were receiving EFV, especially doses of EFV that were higher than or equal to those recommended by the World Health Organization, had more anxiety and more difficulty concentrating at school than children who were receiving alternative ARV medications.[45] Adverse CNS events occurred in 14% of children who received EFV in clinical studies[46] and in 30% of children[47] with plasma EFV concentrations >4 mg/L. Late-onset neurotoxicity, including ataxia and encephalopathy, may occur months to years after initiating EFV. Some events of late-onset neurotoxicity have occurred in people with certain CYP2B6 genetic polymorphisms who received standard doses of EFV. These polymorphisms have been associated with slow metabolism of EFV and increased EFV levels (see the package insert for EFV).

An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the Strategic Timing of AntiRetroviral Treatment (START) Trial, a prospective analysis of adults.[48,49] This association, however, was not found in the analyses of two large observational cohorts,[50,51] and no cases of suicide were reported in a systematic review of randomized trials.[39] In people with preexisting psychiatric conditions, EFV should be used cautiously.

Toxicity: Prolongation of the Corrected QT

The effect of EFV on the QTc interval was evaluated in a study of 58 healthy adult participants; a variety of CYP2B6 polymorphisms was represented within this group. A positive relationship between EFV concentration and QTc prolongation was observed.[1] Clinicians should consider using an alternative to EFV in children who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in children who are at higher risk for Torsades de Pointes.[2]

Therapeutic Drug Monitoring

It is reasonable for a clinician to use TDM to determine whether a person is experiencing toxicity, because the concentration of EFV is higher than the normal therapeutic range for some toxicities.[52,53] Dose reduction or drug discontinuation would be considered appropriate management of drug toxicity. Dose reduction is best performed in consultation with an expert in pediatric HIV. Also, TDM should be considered when administering EFV to children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. TDM should also be considered when using a lower dose of EFV—such as the dose found in EFV 400 mg/3TC/TDF—in children weighing ≥40 kg. Two weeks after initiating EFV in infants and children aged <3 years, clinicians should measure the plasma concentration of EFV. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting the dose. If a child initiated EFV at an investigational dose at <3 years of age, some experts would also measure plasma concentration at age 3 years, after the child transitions to the recommended dose for children aged ≥3 years.

The currently accepted minimum effective concentration of EFV is a mid-dose concentration at 12 hours postdose (C_{12h}) of >1 mg/L in adults, and concentrations of >4.0 mg/L are associated with CNS side effects.[41] However, the validity of using a single target has been called into question.[54] In addition, a lower limit of C_{12h} >0.7mg/L was most predictive of virologic outcome in a study of 180 adults.[55] Findings from a study of 128 African children (aged 1.7–13.5 years) suggest that the concentration at 24 hours (C_{24h}) threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.[56]

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