



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Appendix A: Pediatric Antiretroviral Drug Information

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### **Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors**

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

# Abacavir (ABC, Ziagen) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

## Formulations

**Tablet:** 300 mg (scored)

**Pediatric Oral Solution:** 20 mg/mL

### Generic Formulations:

**Tablet:** 300 mg

### Fixed-Dose Combination Tablets:

- [*Epzicom and Generic*] Abacavir 600 mg/lamivudine 300 mg
- [*Triumeq*] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [*Trizivir*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Abacavir is not approved for use in infants aged <3 months.

### Infant and Child (Aged ≥3 Months) Dose

#### Oral Solution:

- Abacavir 8 mg/kg twice daily (maximum 300 mg per dose) or abacavir 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. **In older children who can be treated with pill formulations, therapy can be initiated with once-daily administration.** In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts while receiving the liquid formulation of abacavir twice daily, the abacavir dose can be changed from twice-daily dosing to once-daily dosing with the liquid or tablet formulations (see text below).

### Weight-Band Dosing for Children and Adolescents Weighing ≥14 kg

Weight	Scored 300-mg Tablet		
	Twice-Daily AM Dose	Twice-Daily PM Dose	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
≥20 kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)
≥25 kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

## Selected Adverse Events

- Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough, shortness of breath).

## Special Instructions

- Test patients for the HLA-B\*5701 allele before starting therapy to predict the risk of HSRs. Patients who test positive for the HLA-B\*5701 allele should not be given abacavir. Patients with no prior HLA-B\*5701 testing who are tolerating abacavir do not need to be tested.
- Warn patients and parents about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of abacavir. Do not re-challenge.**
- Abacavir can be given without regard to food. The oral solution does not require refrigeration.
- When using FDC tablets that contain abacavir, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

## Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.

**Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:**

- Abacavir 300 mg twice daily or 600 mg once daily

**[Epzicom] Abacavir/Lamivudine**

**Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:**

- One tablet once daily

**[Triumeq] Abacavir/Dolutegravir/Lamivudine**

**Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:**

- One tablet once daily
- This fixed-dose combination (FDC) tablet can be used in patients who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.

- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg.

**[Trizivir] Abacavir/Lamivudine/Zidovudine**

**Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:**

- One tablet twice daily

- Eighty-two percent of abacavir metabolites are excreted in urine.
- Abacavir requires a dose adjustment in patients with hepatic insufficiency.
- **Do not use** FDCs such as Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with impaired hepatic function, because the dose of abacavir cannot be adjusted.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with creatinine clearance  $< 50$  mL/min and patients on dialysis, because the dose of lamivudine cannot be adjusted.

## Emtricitabine (FTC, Emtriva) (Last updated September 12, 2019; last reviewed September 12, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Pediatric Oral Solution:** 10 mg/mL

**Capsule:** 200 mg

#### Fixed-Dose Combination Tablets:

- [Atripla and Generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/TDF 300 mg
- [Descovy] Emtricitabine 200 mg/TAF 25 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/TAF 25 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TDF 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [Truvada low-strength tablets]
  - Emtricitabine 100 mg/TDF 150 mg
  - Emtricitabine 133 mg/TDF 200 mg
  - Emtricitabine 167 mg/TDF 250 mg
- [Truvada] Emtricitabine 200 mg/TDF 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

### Dosing Recommendations

#### Neonatal and Infant (Aged 0 to <3 Months) Dose

*Oral Solution:*

- Emtricitabine 3 mg/kg once daily

#### Child (Aged ≥3 Months) and Adolescent Dose

*Oral Solution:*

- Emtricitabine 6 mg/kg once daily (maximum 240 mg per dose). The maximum dose of oral solution is higher than the capsule dose because the oral solution showed 20% lower plasma exposure during pediatric pharmacokinetic analysis.

*Capsules (For Patients Weighing >33 kg):*

- Emtricitabine 200 mg once daily

#### Adult Dose

*Oral Solution for Those Unable to Swallow*

*Capsules:*

- Emtricitabine 240 mg (24 mL) once daily

### Selected Adverse Events

- Severe acute exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV coinfection who discontinue emtricitabine
- Hyperpigmentation/skin discoloration on palms and/or soles

### Special Instructions

- Although emtricitabine can be administered without regard to food, there are food requirements for some FDC tablet formulations that contain emtricitabine.
- Emtricitabine oral solution can be kept at room temperature, up to 77°F (25°C), if used within 3 months; refrigerate for long-term storage.
- Before using emtricitabine, screen patients for HBV.

### Capsules:

- Emtricitabine 200 mg once daily

### [Atripla and Generic] Efavirenz/Emtricitabine/TDF

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

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

### [Biktarvy] Bictegravir/Emtricitabine/TAF

**Child (Weighing  $< 25$  kg) Dose:**

- There are currently no data available on the appropriate dose of Biktarvy in children aged  $< 6$  years and weighing  $< 25$  kg. **Studies are currently being conducted to identify the appropriate dose for this age and weight group.**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily **with or without food** in antiretroviral therapy (ART)-naive patients. This dose of Biktarvy can also be used to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.
- See the [bictegravir](#) section for additional information.

### [Complera] Emtricitabine/Rilpivirine/TDF

*Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily in ART-naive patients who have baseline plasma HIV RNA  $\leq 100,000$  copies/mL. This dose of Complera can also be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no history of virologic failure or resistance to the individual components of Complera.
- Administer with a meal of at least 500 calories.

### [Descovy] Emtricitabine/TAF

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- **Body Weight 25 to  $< 35$  kg:** One tablet once

## Metabolism/Elimination

- No cytochrome P450 interactions
- Eighty-six percent of emtricitabine is excreted in urine. Emtricitabine may compete with other compounds that undergo renal elimination.

### Emtricitabine Dosing in Patients with Renal Impairment:

- Decrease the dose of emtricitabine in patients with impaired renal function. Consult the manufacturer's prescribing information for recommended dose adjustments.
- Do not use the FDC Atripla in patients with creatinine clearance (CrCl)  $< 50$  mL/min or in patients who require dialysis.
- Do not use the FDCs Truvada or Biktarvy in patients with CrCl  $< 30$  mL/min. Do not use Truvada in patients who require dialysis.
- Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Monitor frequently for adverse events, because rilpivirine concentrations may increase in patients with severe renal impairment or end-stage renal disease.
- Stribild should not be initiated in patients with estimated CrCl  $< 70$  mL/min and should be discontinued in patients with estimated CrCl  $< 50$  mL/min.
- TAF-containing formulations are not recommended for use in patients with estimated CrCl  $< 30$  mL/min.

daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., Descovy can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).

- *Body Weight  $\geq 35$  kg*: One tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

#### **[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily with food in ART-naive patients. This dose of Genvoya can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

#### **[Odefsey] Emtricitabine/Rilpivirine/TAF**

*Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily in ART-naive patients with HIV RNA  $\leq 100,000$  copies per mL. This dose of Odefsey can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

#### **[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg with a Sexual Maturity Rating of 4 or 5) and Adult Dose:*

- One tablet once daily with food in ART-naive patients. This dose of Stribild can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components

of Stribild.

**[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Aged <18 Years) Dose:*

- Symtuza has not been approved by the FDA for use in patients aged <18 years.

*Adult (Aged ≥ 18 Years) Dose:*

- One tablet taken once daily with food in ARV-naive patients or in patients who have been virologically suppressed for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

**[Truvada] Emtricitabine/TDF (FTC/TDF):**

*Child, Adolescent, and Adult Dose:*

**Truvada Dosing Table**

<b>Body Weight</b>	<b>Truvada Tablet Once Daily</b>
17 kg to <22 kg	One FTC/TDF 100 mg/150 mg tablet
22 kg to <28 kg	One FTC/TDF 133 mg/200 mg tablet
28 kg to <35 kg	One FTC/TDF 167 mg/250 mg tablet
≥35 kg and Adults	One FTC/TDF 200 mg/300 mg tablet



## Lamivudine (3TC, Epivir) (Last updated September 12, 2019; last reviewed September 12, 2019)

For additional information, see Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

#### Pediatric Oral Solution:

- [Epivir] 10 mg/mL
- [Epivir HBV]<sup>a</sup> 5 mg/mL

#### Tablets:

- [Epivir] 150 mg (scored) and 300 mg
- [Epivir HBV]<sup>a</sup> 100 mg

#### Generic Formulations:

- 100 mg, 150 mg, and 300 mg tablets
- Fixed-dose combination tablet containing lamivudine 150 mg/zidovudine 300 mg

#### Fixed-Dose Combination Tablets:

- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Combivir] Lamivudine 150 mg/zidovudine 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg
- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Epzicom] Abacavir 600 mg/lamivudine 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg
- [Temixys] Lamivudine 300 mg/TDF 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#) for information about using lamivudine for the prevention of perinatal HIV transmission.

#### Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to <4 Weeks) Dose

*Oral Solution:*

- Lamivudine 2 mg/kg twice daily

#### Infant and Child Dose

**Note:** In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine **is not recommended**. Patients can be transitioned to once-daily treatment with the oral solution when they have been stable

### Selected Adverse Events

- Severe exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV coinfection who discontinue lamivudine.

### Special Instructions

- Lamivudine can be given without regard to food.
- Store lamivudine oral solution at room temperature.
- Screen patients for HBV infection before administering lamivudine.

### Metabolism/Elimination

- Dose adjustment required in patients with

on twice-daily treatment for 36 weeks and are aged  $\geq 3$  years. Please see the note below and refer to the text for more detail.

*Aged  $\geq 4$  Weeks to  $< 3$  Months:*

- Lamivudine 4 mg/kg twice daily of the oral solution

*Aged  $\geq 3$  Months to  $< 3$  Years:*

- Lamivudine 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)

*Aged  $\geq 3$  Years:*

- Lamivudine 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose); *or*
- 10 mg/kg once daily of the oral solution (maximum 300 mg per dose)

*Weighing  $\geq 14$  kg and Able to Swallow Pills:*

- Weight-band dosing (see table below; dose is approximately lamivudine 5 mg/kg/day twice daily or lamivudine 10 mg/kg once daily)

**Weight-Band Dosing for the Scored, 150-mg Lamivudine Tablet in Children Weighing  $\geq 14$  kg**

Weight	Twice-Daily AM Dose	Twice-Daily PM Dose	Once-Daily Dose
14 kg to $< 20$ kg	$\frac{1}{2}$ tablet (75 mg)	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)
$\geq 20$ kg to $< 25$ kg	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)	$1\frac{1}{2}$ tablets (225 mg)
$\geq 25$ kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets (300 mg)

**Note:** The scored tablet is the preferred formulation for pediatric patients weighing  $\geq 14$  kg who can swallow a tablet.

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching from twice-daily dosing to once-daily dosing of lamivudine (using the oral solution or tablets) in children aged  $\geq 3$  years who have been clinically stable for 36 weeks with undetectable viral loads and stable CD4 T lymphocyte counts. Clinicians should choose a reasonable, once-daily regimen using the once-daily dose of lamivudine indicated above (approximately lamivudine 10 mg/kg, with a maximum of lamivudine 300 mg once daily).

**Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:**

- Lamivudine 150 mg twice daily; *or*
- Lamivudine 300 mg once daily

renal insufficiency.

- FDC tablets should not be used in patients who are on dialysis or who have creatinine clearance  $< 50$  mL/min or impaired hepatic function.

### **[Cimduo] Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily

### **[Combivir and Generic] Lamivudine/Zidovudine**

*Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:*

- One tablet twice daily

### **[Delstrigo] Doravirine/Emtricitabine/TDF**

*Adult Dose:*

- One tablet once daily
- Not studied in children or adolescents (see [doravirine](#) section)

### **[Dovato] Dolutegravir/Lamivudine**

*Adult Dose:*

- One tablet once daily with or without food as a complete antiretroviral (ARV) regimen in adults with no ARV treatment history and no known substitutions associated with resistance to the individual components of Dovato.
- Dovato is not approved for use in children or adolescents.

### **[Epzicom] Abacavir/Lamivudine**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily

### **[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily on an empty stomach

### **[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily on an empty stomach

**Note:** Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1 to 3) and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 weighing  $\geq 40$  kg. Therapeutic drug monitoring is suggested by some Panel

members when Symfi Lo is used in pediatric patients weighing  $\geq 40$  kg. See the [efavirenz](#) section for more information.

#### **[Temixys] Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily

#### **[Triumeq] Abacavir/Dolutegravir/Lamivudine**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily
- This FDC tablet can be used in patients who are ARV-naïve or ARV-experienced (but integrase strand transfer inhibitor-naïve) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg.

#### **[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine**

*Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:*

- One tablet twice daily

<sup>a</sup> Eпивir HBV oral solution and tablets contain a lower amount of lamivudine than Eпивir oral solution and tablets. The amount of lamivudine in the Eпивir HBV solution and tablet was based on dosing for treatment of HBV infection in people without HIV coinfection. If Eпивir HBV is used in patients with HIV, the higher dose indicated for HIV therapy should be used as part of an appropriate combination regimen.

## Tenofovir Alafenamide (TAF, Vemlidy) (Last updated September 12, 2019; last reviewed September 12, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Tablets:** 25 mg<sup>a</sup>

#### Fixed-Dose Combination Tablets

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg
- [Descovy] Emtricitabine 200 mg/TAF 25 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/TAF 25 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

### Dosing Recommendations

#### [Biktarvy] Bictegravir/Emtricitabine/TAF

*Child (Weighing <25 kg) Dose:*

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg. **Studies are currently being conducted to identify the appropriate dose for this age and weight group.**

*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*

- One tablet once daily **with or without food** in antiretroviral (ARV) therapy-naïve patients. This dose of Biktarvy can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.
- See the [bictegravir section](#) for additional information.

#### [Descovy] Emtricitabine/TAF

*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*

- **Body Weight 25 kg to <35 kg:** One tablet once daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e.,

### Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

### Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before using TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TAF is stopped.
- The Food and Drug Administration does not recommend using Genvoya with other ARV drugs, but this FDC has safely been used with darunavir.<sup>1</sup> Descovy can be safely used with cobicistat-boosted or ritonavir-boosted darunavir or atazanavir in patients weighing ≥35 kg.<sup>2</sup>
- **Do not use** Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated with cobicistat.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal) because it contains rilpivirine.

Descovy can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).

- *Body Weight*  $\geq 35$  kg: One tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

#### **[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily with food in ARV-naive patients. This dose of Genvoya can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

#### **[Odefsey] Emtricitabine/Rilpivirine/TAF**

*Child and Adolescent (Aged  $\geq 12$  Years Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily with a meal in ARV-naive patients with HIV RNA  $\leq 100,000$  copies/mL. This dose of Odefsey can also be used to replace a current, stable ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.

#### **[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF**

*Adult (Aged  $\geq 18$  Years) Dose:*

- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

### **Metabolism/Elimination**

- TAF undergoes renal excretion.

#### **TAF Dosing in Patients with Hepatic Impairment:**

- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but they should not be used in patients with severe hepatic impairment because they have not been studied in that group.

#### **TAF Dosing in Patients with Renal Impairment:**

- The TAF 25-mg tablet<sup>a</sup> **is not recommended** for use in patients with estimated creatinine clearance (CrCl)  $< 15$  mL/min. TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl  $< 30$  mL/min.

<sup>a</sup> TAF 25-mg tablets (Vemlidy) are approved by the FDA for treatment of HBV. In select circumstances, TAF might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

# Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

## Formulations

**Tablets:** 150 mg, 200 mg, 250 mg, and 300 mg

**Oral Powder:** 40 mg per 1 g of oral powder (1 level scoop, measured with supplied dosing scoop = 1 g oral powder)

### Fixed-Dose Combination Tablets

- [Atripla and Generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Cimduo] Lamivudine 300 mg/TDF 300 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/TDF 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TDF 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg
- [Temixys] Lamivudine 300 mg/TDF 300 mg
- [Truvada low-strength tablet]
  - Emtricitabine 100 mg/TDF 150 mg
  - Emtricitabine 133 mg/TDF 200 mg
  - Emtricitabine 167 mg/TDF 250 mg
- [Truvada tablet] Emtricitabine 200 mg/TDF 300 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- TDF has not been approved by the Food and Drug Administration or recommended for use in neonates and infants aged <2 years.

### Child (Aged ≥2 Years to <12 Years) Dose:<sup>a</sup>

- TDF 8 mg/kg/dose once daily

### TDF Oral Powder Dosing Table

Body Weight	TDF Oral Powder Once-Daily Scoops of Powder
10 kg to <12 kg	2 scoops (80 mg)
12 kg to <14 kg	2.5 scoops (100 mg)
14 kg to <17 kg	3 scoops (120 mg)
17 kg to <19 kg	3.5 scoops (140 mg)
19 kg to <22 kg	4 scoops (160 mg)
22 kg to <24 kg	4.5 scoops (180 mg)
24 kg to <27 kg	5 scoops (200 mg)
27 kg to <29 kg	5.5 scoops (220 mg)
29 kg to <32 kg	6 scoops (240 mg)
32 kg to <34 kg	6.5 scoops (260 mg)
34 kg to <35 kg	7 scoops (280 mg)
≥35 kg	7.5 scoops (300 mg)

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density<sup>a</sup>

## Special Instructions

- Do not crush tablets. TDF oral powder formulation is available for patients who are unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = TDF 40 mg.
- Mix TDF oral powder with 2 to 4 oz. of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with liquid. The powder may float on the top even after vigorous stirring.
- Although TDF can be administered without

## TDF Tablet Dosing Table for Patients Aged $\geq 2$ Years and Weighing $\geq 17$ kg

Body Weight	TDF Tablet Once Daily
17 kg to <22 kg	150 mg
22 kg to <28 kg	200 mg
28 kg to <35 kg	250 mg
$\geq 35$ kg	300 mg

### Child and Adolescent (Weighing $\geq 35$ kg)<sup>a</sup> and Adult Dose:

- TDF 300 mg once daily

### [Atripla and Generic] Efavirenz/Emtricitabine/TDF Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose:

- One tablet once daily
- Take on an empty stomach

### [Cimduo] Lamivudine/TDF

#### Child and Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily

### [Complera] Emtricitabine/Rilpivirine/TDF

#### Child and Adolescent (Aged $\geq 12$ Years and Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily in treatment-naive adults with baseline viral loads  $\leq 100,000$  copies/mL. This dose of Complera can also be used in virologically suppressed adults who are currently on their first or second regimen and who have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.
- Administer with a meal of at least 500 calories.

### [Delstrigo] Doravirine/Emtricitabine/TDF

#### Adult Dose:

- One tablet once daily
- Not studied in children or adolescents (see [doravirine](#) section)

### [Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF

#### Adolescent (Weighing $>35$ kg with a Sexual Maturity Rating [SMR] of 4 or 5) and Adult Dose:

- One tablet once daily in treatment-naive adults. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV

regard to food, food requirements vary depending on the other ARV drugs contained in a fixed-dose combination (FDC) tablet. Food requirements are listed with dosing recommendations and in [Table 2 of the Drug Appendix](#).

- Measure serum creatinine and perform a urine dipstick test for protein and glucose before starting a TDF-containing regimen. Serum creatinine should be monitored and urine should be tested for protein and glucose at intervals (see [Table 15i](#)) during continued therapy. Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function and hepatitis B viral load for several months after therapy with TDF is stopped.
- When using FDC tablets, see other drug sections for special instructions and additional information about the individual drug components.
- Tenofovir alafenamide (TAF) is associated with less bone and renal toxicity than TDF, but it has equal antiviral efficacy. **Do not use TAF and TDF together.** Consider switching from TDF to TAF in appropriate clinical settings.

## Metabolism/Elimination

- TDF is renally excreted.

### TDF Dosing in Patients with Renal Insufficiency:

- TDF dose should be decreased in patients with impaired renal function (creatinine clearance [CrCl]  $<50$  mL/min). Consult manufacturer's prescribing information for adjustment of dose in accordance with CrCl.
- The FDCs Atripla, Complera, and Symfi Lo should not be used in patients with CrCl  $<50$  mL/min or in patients requiring dialysis.
- The FDC Truvada should not be used in patients with CrCl  $<30$  mL/min or in patients who require dialysis.
- The FDC Stribild should not be initiated in patients with estimated CrCl  $<70$  mL/min and should be discontinued in patients with



RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.

- Administer with food.

**[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

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

- One tablet once daily
- Take on an empty stomach

**[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

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

- One tablet once daily
- Take on an empty stomach

**Note:** Symfi Lo has not been studied in children (SMR 1 to 3) and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents SMR 1-3 who weigh ≥40 kg. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing ≥40 kg. See the [efavirenz](#) section for more information.

**[Temixys] Lamivudine/TDF**

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

- One tablet once daily

**[Truvada] Emtricitabine/TDF (FTC/TDF)**

*Child, Adolescent, and Adult Dose:*

**Truvada Dosing Table**

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	One FTC/TDF 100 mg/150 mg tablet
22 kg to <28 kg	One FTC/TDF 133 mg/200 mg tablet
28 kg to <35 kg	One FTC/TDF 167 mg/250 mg tablet
≥35 kg and Adults	One FTC/TDF 200 mg/300 mg tablet

estimated CrCl <50 mL/min.

- Stribild should not be used in patients with severe hepatic impairment.

<sup>a</sup> See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

## Zidovudine (ZDV, Retrovir) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Capsule:** 100 mg

**Tablet:** 300 mg

**Syrup:** 10 mg/mL

**Concentrate for Injection or Intravenous Infusion:** 10 mg/mL

### Generic Formulations:

- Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

### Fixed-Dose Combination Tablets:

- [*Combivir and Generic*] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [*Trizivir and Generic*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

### Dosing Recommendations

**Note:** Zidovudine is frequently used in neonates to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and [Table 12](#) for information about using zidovudine to prevent perinatal transmission.

#### Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth<sup>a</sup>

Gestational Age at Birth	Oral Zidovudine Dose								
≥35 weeks	<p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"><li>• Zidovudine 4 mg/kg orally twice daily; <i>or</i></li><li>• Alternative simplified weight-band dosing</li></ul> <p><u>Simplified Weight Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth:</u></p> <p><b>Note:</b> The doses in this table provide approximately zidovudine 4 mg/kg orally twice daily from birth to age 4 weeks.</p> <table border="1"><thead><tr><th>Weight Band</th><th>Volume of Zidovudine 10 mg/mL Oral Syrup Twice Daily</th></tr></thead><tbody><tr><td>2 kg to &lt;3 kg</td><td>1 mL</td></tr><tr><td>3 kg to &lt;4 kg</td><td>1.5 mL</td></tr><tr><td>4 kg to &lt;5 kg</td><td>2 mL</td></tr></tbody></table> <p>Aged &gt;4 Weeks:</p> <ul style="list-style-type: none"><li>• Zidovudine 12 mg/kg orally twice daily</li></ul>	Weight Band	Volume of Zidovudine 10 mg/mL Oral Syrup Twice Daily	2 kg to <3 kg	1 mL	3 kg to <4 kg	1.5 mL	4 kg to <5 kg	2 mL
Weight Band	Volume of Zidovudine 10 mg/mL Oral Syrup Twice Daily								
2 kg to <3 kg	1 mL								
3 kg to <4 kg	1.5 mL								
4 kg to <5 kg	2 mL								

### Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia; macrocytosis with or without anemia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of zidovudine) and myositis

### Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- When using fixed-dose combination (FDC) tablets that contain zidovudine, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

### Metabolism/Elimination

- Zidovudine is eliminated primarily by

Gestational Age at Birth	Oral Zidovudine Dose
≥30 weeks to <35 weeks	<p>Birth to Age 2 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 2 mg/kg orally twice daily</li> </ul> <p>Aged 2 Weeks to 6 to 8 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;6 Weeks to 8 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 12 mg/kg orally twice daily</li> </ul>
<30 weeks	<p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 2 mg/kg orally twice daily</li> </ul> <p>Aged 4 Weeks to 8 to 10 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;8 Weeks to 10 Weeks:</p> <ul style="list-style-type: none"> <li>Zidovudine 12 mg/kg orally twice daily</li> </ul>

**Note:** For infants who are unable to tolerate oral agents, the intravenous dose should be 75% of the oral dose, but the dosing interval should remain the same.

### Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

#### Zidovudine Weight-Based Dosing

Body Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

#### Alternative Body Surface Area Dosing

*Oral:*

- Zidovudine 180 mg to 240 mg per m<sup>2</sup> of body surface area every 12 hours

#### Adolescent (Aged ≥18 Years) and Adult Dose:

- Zidovudine 300 mg twice daily

#### [Combivir and Generic] Lamivudine/Zidovudine

**Child and Adolescent (Weighing ≥30 kg) and Adult Dose:**

- One tablet twice daily

#### [Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

**Child and Adolescent (Weighing ≥30 kg) and Adult Dose:**

- One tablet twice daily

hepatic metabolism. The major metabolite is zidovudine glucuronide, which is renally excreted.

- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

#### Zidovudine Dosing in Patients with Renal Impairment:

- A zidovudine dose adjustment is required in patients with renal insufficiency.

#### Zidovudine Dosing in Patients with Hepatic Impairment:

- The dose of zidovudine may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min or in patients who are on dialysis or who have impaired hepatic function.

<sup>a</sup> For premature infants who are diagnosed with HIV infection, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

## **Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)**

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence,)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant)

## Doravirine (DOR, Pifeltro) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Tablet:** 100 mg

#### Fixed-Dose Combination Tablet:

- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg

### Dosing Recommendations

#### Child and Adolescent Dose:

- Doravirine is not approved for use in children or adolescents aged <18 years.

#### Adult (Aged ≥18 Years) Dose

##### Antiretroviral-Naive Patients:

- Doravirine 100 mg once daily

#### [Delstrigo] Doravirine/Lamivudine/TDF

##### Adult (Aged ≥18 Years) Dose:

- One tablet once daily

### Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

### Special Instructions

- Doravirine can be taken with or without food.
- Do not use doravirine with other non-nucleoside reverse transcriptase inhibitors.
- When doravirine is coadministered with rifabutin, the dose of doravirine should be increased to 100 mg twice daily. When doravirine/lamivudine/TDF (Delstrigo) is coadministered with rifabutin, an additional dose of freestanding doravirine (Pifeltro) needs to be administered approximately 12 hours later.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains lamivudine and TDF. Severe acute exacerbation of HBV can occur when lamivudine or TDF is discontinued; therefore, hepatic function should be monitored for several months after halting therapy with lamivudine or TDF.
- See the lamivudine and TDF sections of the Drug Appendix for special instructions and additional information about the individual drug components of Delstrigo.

### Metabolism/Elimination

- Doravirine is metabolized by the enzyme cytochrome P450 3A.

- Doravirine has multiple interactions with several drugs (see text below).

#### Doravirine Dosing in Patients with Hepatic Impairment:

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in patients with severe hepatic impairment.

#### Doravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required when using doravirine in patients with mild, moderate, or severe renal impairment. Doravirine use has not been studied in patients with end-stage renal disease nor in patients on dialysis.
- Doravirine administered with lamivudine and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

## Efavirenz (EFV, Sustiva) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Capsules:** 50 mg, 200 mg

**Tablet:** 600 mg

#### Generic Formulations:

- 50 mg capsules
- 200 mg capsules
- 600 mg tablets

#### Fixed-Dose Combination Tablets:

- [Atripla and Generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg

### Dosing Recommendations

#### Neonatal Dose:

- Efavirenz is not approved for use in neonates.

#### Pediatric Dose

- Efavirenz 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  $\geq 3.5$  kg:*

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of efavirenz in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.
- **Note:** If the use of efavirenz is unavoidable due to a clinical situation, the Panel suggests using investigational doses of efavirenz in this age group (see investigational dosing [Table A](#) in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of cytochrome P450 (CYP) 2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring (TDM) should be used and efavirenz plasma concentration should be measured 2 weeks after initiation. If a child initiated efavirenz at an investigational dose while <3 years of age, some experts would also measure plasma

### Selected Adverse Events

- Rash, which is generally mild and transient and appears to be more common in children than in adults
- Central nervous system (CNS) symptoms such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- Use of efavirenz may produce false-positive results with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation

### Special Instructions

- Efavirenz can be swallowed as a whole capsule/tablet or 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 efavirenz, Atripla, **Symfi**, or Symfi Lo on an empty stomach. Avoid administration with a high-fat meal, because this has the potential to increase absorption.
- When using fixed-dose combination (FDC) tablets, see other drug sections in the

concentration at age 3 years after the child transitions to the recommended dose for children aged  $\geq 3$  years (see the Therapeutic Drug Monitoring section in the text below). When making a dose adjustment based on efavirenz concentrations, consultation with an **expert in pediatric HIV infection** is recommended.

*Children Aged  $\geq 3$  Years and Weighing  $\geq 10$  kg:*

#### Once-Daily Doses of Efavirenz by Weight

Weight	Efavirenz Dose <sup>a,b</sup>
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
$\geq 40$ kg	600 mg

<sup>a</sup> 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).

<sup>b</sup> Some experts recommend a dose of efavirenz 367 mg/m<sup>2</sup> body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see Pediatric Use in text below for details). Weight bands approximate a dose of efavirenz 367 mg/m<sup>2</sup>, with a maximum dose of 600 mg.

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:**

- Efavirenz 600 mg once daily

**[Atripla] Efavirenz 600 mg/Emtricitabine/TDF**

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:**

- One tablet once daily
- Take on an empty stomach

**[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:**

- One tablet once daily
- Take on an empty stomach

**[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

**Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:**

- One tablet once daily
- Take on an empty stomach

[Drug Appendix](#) for special instructions and additional information about the individual drug components.

- The Food and Drug Administration cautions that efavirenz should not be used during the first trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the [Perinatal Guidelines](#) do not restrict use of efavirenz in female adolescents and adults who are pregnant or may become pregnant.

#### Instructions for Use of Efavirenz Capsule as a Sprinkle Preparation with Food or Formula:

- Hold capsule horizontally over a small container and carefully twist to 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) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

#### Metabolism/Elimination

- **CYP2B6 is the primary enzyme for efavirenz metabolism.**
- Cytochrome P450 (CYP) 3A and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Efavirenz **is not recommended** for patients with moderate or severe hepatic impairment.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450, with slower metabolizers at higher risk of toxicity (see [Therapeutic Drug Monitoring](#) in the text below for information about the management of mild or moderate toxicity).

#### Atripla, Symfi, and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are FDC products and TDF, **lamivudine**, and emtricitabine require dose adjustments based on renal function, Atripla, **Symfi**, and Symfi Lo should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.



**Note:** Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1–3), and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 who weigh  $\geq 40$  kg. TDM is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh  $\geq 40$  kg.

# Etravirine (ETR, Intelence) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

## Formulations

**Tablets:** 25 mg, 100 mg, 200 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Etravirine is not approved for use in neonates/infants.

#### Child Dose:

- Etravirine is not approved for use in children aged <2 years. Studies in infants and children aged 2 months to 2 years are under way.

#### Etravirine Dosing Table for Antiretroviral-Experienced Children and Adolescents Aged 2 Years to 18 Years and Weighing $\geq 10$ kg

Body Weight	Dose
10 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
$\geq 30$ kg	200 mg twice daily

#### Adult Dose for Antiretroviral-Experienced Patients:

- 200 mg twice daily with food

### Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

### Special Instructions

- Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. Always administer etravirine with food. The type of food does not affect the exposure to etravirine.

### Instructions for Dispersing Etravirine Tablets in Liquid:

- Patients who are unable to swallow etravirine tablets may disperse the tablets in liquid.
- Place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication, and stir well until the water looks milky. Add approximately 15 mL (1 tablespoon) of additional liquid. Water may be used, but other liquids, such as orange juice or milk, may improve the taste of the medication. Patients should not place the tablets in orange juice or milk without first adding water. Warm beverages (with temperatures  $>104^{\circ}\text{F}$  or  $>40^{\circ}\text{C}$ ) or carbonated beverages should be avoided.
- Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Etravirine tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.

## **Metabolism/Elimination**

- Etravirine is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.
- Etravirine is involved in multiple interactions with antiretroviral agents and other drugs (see text below).

### **Etravirine Dosing in Patients with Hepatic Impairment:**

- No dose adjustment is required when using etravirine in patients with mild or moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

### **Etravirine Dosing in Patients with Renal Impairment:**

- No dose adjustment is required for patients with renal impairment.

# Nevirapine (NVP, Viramune) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

## Formulations

**Tablets:** Immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg

**Suspension:** 10 mg/mL

### Generic Formulations:

- Immediate-release 200 mg tablets
- Extended-release (XR) 400 mg tablets

**Note:** While the suspension formulation of brand-name nevirapine (Viramune) is available, it is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

## Dosing Recommendations

**Note:** Nevirapine is often used to prevent perinatal transmission of HIV. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for information about nevirapine dosing in neonates aged  $\leq 1$  days.

### Child and Adolescent Dose:

- **Note:** In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged  $< 2$  years.<sup>a</sup>

### Immediate-Release Tablets and Suspension Formulations

#### Gestational Age 34 Weeks–37 Weeks:

- Nevirapine 4 mg/kg per dose twice daily for the first week, increasing to nevirapine 6 mg/kg per dose twice daily thereafter (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the Food and Drug Administration (FDA).

#### Gestational Age $\geq 37$ Weeks to Age $< 1$ Month:

- Nevirapine 6 mg/kg per dose twice daily (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the FDA.
- See the [Special Considerations for Dosing: Neonates and Premature Infants](#) section below.

#### Aged $\geq 1$ Month to $< 8$ Years:

- Nevirapine 200 mg/m<sup>2</sup> of body surface area per dose twice daily after lead-in dosing.<sup>a</sup> In children aged  $\leq 2$  years, some experts initiate

## Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis<sup>b</sup>
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

## Special Instructions

- Shake suspension well before administering and store at room temperature.
- Nevirapine can be given without regard to food.
- Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14 day lead-in period, do not increase dose until rash resolves (see [Major Toxicities](#) below).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for  $> 14$  days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see [Dosing Considerations: Lead-In Requirement](#) below).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see [Major Toxicities](#) below).

nevirapine without lead-in dosing (maximum dose of immediate-release tablets is 200 mg twice daily).

#### *Aged ≥8 Years:*

- Nevirapine 120–150 mg per m<sup>2</sup> of body surface area per dose twice daily after lead-in dosing<sup>a</sup> (maximum dose of immediate-release tablets is nevirapine 200 mg twice daily).
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose can be left static to achieve the appropriate mg-per-m<sup>2</sup> dose as the child grows, as long as there are no adverse effects.

#### **Extended-Release Tablets**

##### *Aged ≥6 Years:*

- Patients aged ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing.<sup>a</sup>

#### **Body Surface Area Dosing for Nevirapine Extended-Release Tablets**

<b>Body Surface Area Range</b>	<b>Nevirapine Extended-Release Tablets</b>
0.58 m <sup>2</sup> to 0.83 m <sup>2</sup>	200 mg once daily (two 100-mg tablets)
0.84 m <sup>2</sup> to 1.16 m <sup>2</sup>	300 mg once daily (three 100-mg tablets)
≥1.17 m <sup>2</sup>	400 mg once daily (one 400-mg tablet)

##### *Adolescent and Adult Dose:*

- Nevirapine 200 mg twice daily or 400 mg extended release once daily after lead-in dosing.<sup>a,b</sup>

#### **Nevirapine Used in Combination with Lopinavir/Ritonavir:**

- A higher dose of lopinavir/ritonavir may be needed (see the [Lopinavir/ritonavir](#) section).

#### **Metabolism/Elimination**

- Nevirapine is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a nevirapine dose is eliminated in urine as UGT-derived glucuronidated metabolites.

#### **Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:**

- An additional dose of nevirapine should be given following each dialysis session.

#### **Nevirapine Dosing in Patients with Hepatic Impairment:**

- Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

<sup>a</sup> Nevirapine is usually initiated at a lower dose that is increased in a stepwise fashion. Nevirapine induces CYP metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the immediate-release formulation once daily instead of twice daily for the first 14 days of therapy. If there are no rash or other adverse effects after 14 days of therapy, increase the dose of nevirapine to the age-appropriate full dose of the immediate-release formulation administered twice daily. **For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is nevirapine 200 mg per m<sup>2</sup> of body surface area once daily for the first 14 days, followed by nevirapine 200 mg per m<sup>2</sup> of body surface area twice daily thereafter.** However, in children aged ≤2 years, some experts initiate nevirapine without lead-in dosing (see [Dosing Considerations: Lead-In Requirement](#) and [Special Considerations for Dosing: Neonates and Premature Infants](#) below). In patients who are already receiving the full twice-daily dose of immediate-release nevirapine, extended-release tablets can be used without the lead-in period. Patients must swallow nevirapine extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of nevirapine at the same time.** The dose should not exceed 400 mg daily.

<sup>b</sup> Symptomatic hepatitis, including fatal hepatic necrosis, occurs at a significantly higher frequency in antiretroviral (ARV)-naive women with pre-nevirapine CD4 T lymphocyte (CD4) cell counts >250 cells/mm<sup>3</sup> and in ARV-naive men with pre-nevirapine CD4 counts >400 cells/mm<sup>3</sup>. Nevirapine **should not be initiated** in these patients unless the benefit clearly outweighs the risk.

# Rilpivirine (RPV, Edurant) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

## Formulations

**Tablets:** 25 mg

### Fixed-Dose Combination Tablets:

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide (TAF) 25 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Rilpivirine is not approved for use in neonates or infants.

### Children Aged <12 Years:

- Rilpivirine is not approved by the Food and Drug Administration for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

### Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

- Rilpivirine 25 mg once daily **with a meal** in antiretroviral (ARV) treatment-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to rilpivirine and other ARV drugs in the new regimen.

### [Complera] Emtricitabine/Rilpivirine/TDF

#### Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:

#### Adult Dose:

- One tablet once daily **with a meal** in ARV treatment-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (defined as HIV RNA <50 copies per mL) for ≥6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Complera.

### [Juluca] Dolutegravir/Rilpivirine

#### Adult Dose:

- One tablet once daily with a meal as a

## Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction/Rash with Eosinophilia and Systemic Symptoms)
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

## Special Instructions

- **Do not start** rilpivirine in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- **Do not use** rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** rilpivirine with proton pump inhibitors.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- **H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.**
- Use rilpivirine with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see [CredibleMeds](#)).
- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and

complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) on a stable ARV regimen for  $\geq 6$  months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.

- Not approved for use in children or adolescents (see Simplification of Treatment section below).

**[Odefsey] Emtricitabine/Rilpivirine/TAF**  
**Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose:**

- One tablet once daily with a meal as initial therapy in ARV treatment-naive patients with HIV RNA  $\leq 100,000$  copies per mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for  $\geq 6$  months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Odefsey.

additional information about the individual components of the FDC.

### **Metabolism/Elimination**

- Cytochrome P450 (CYP) 3A substrate.

### **Rilpivirine Dosing in Patients with Hepatic Impairment:**

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

### **Rilpivirine Dosing in Patients with Renal Impairment:**

- No dose adjustment is necessary in patients with mild or moderate renal impairment.
- The FDC drugs Complera and Odefsey **should not be used** in patients with creatinine clearance <50 mL/min or <30 mL/min, respectively, or in patients who require dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease, so monitoring for adverse events is especially important in these patients.
- When using Complera, see the [TDF section](#) of the guidelines; when using Odefsey, see the [TAF section](#).

## **Protease Inhibitors (PIs)**

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)



# Atazanavir (ATV, Reyataz) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

## Formulations

**Powder Packet:** 50 mg/packet

**Capsules:** 150 mg, 200 mg, and 300 mg

### Generic Formulations

**Capsules:** 150 mg, 200 mg, 300 mg

### Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg

**Capsules and powder packets are not interchangeable.**

## Dosing Recommendations

### Neonate Dose:

- Atazanavir is not approved for use in neonates and infants aged <3 months. Atazanavir **should not be administered** to neonates due to risks associated with hyperbilirubinemia (kernicterus).

### Infant and Child Dose

#### Powder Formulation:<sup>a</sup>

- The powder formulation must be administered with ritonavir.
- The powder formulation is not approved for use in infants aged <3 months or weighing <5 kg.

#### Atazanavir Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥5 kg<sup>a</sup>

Weight	Once-Daily Dose
5 kg to <15 kg	Atazanavir 200 mg (four packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food
15 kg to <25 kg <sup>b</sup>	Atazanavir 250 mg (five packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

#### Capsule Formulation:<sup>a</sup>

- Capsules are not approved for use in children aged <6 years or weighing <15 kg.

## Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (occurs primarily with ritonavir boosting)

## Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets **are not interchangeable**.
- Do not open capsules.
- Because atazanavir can prolong the PR interval, use atazanavir with caution in patients with pre-existing cardiac conduction system disease or with other drugs that are known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the [atazanavir package insert](#)).
- The plasma concentration, and therefore the therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is coadministered with proton-

## Atazanavir Capsule Dosing Table for Children and Adolescents Aged $\geq 6$ Years and Weighing $\geq 15$ kg

Weight	Once-Daily Dose
<15 kg	Capsules not recommended
15 kg to <35 kg	Atazanavir/ritonavir <sup>c</sup> 200 mg/100 mg, both once daily with food
$\geq 35$ kg	Atazanavir/ritonavir <sup>c</sup> 300 mg/100 mg, both once daily with food

### For Treatment-Naive Children and Adolescents Who Do Not Tolerate Ritonavir:

- Atazanavir powder is not an option, since it must be administered with ritonavir. For the capsule formulation, while the Food and Drug Administration (FDA) does not recommend the use of unboosted atazanavir in children aged <13 years, adolescents aged  $\geq 13$  years weighing  $\geq 40$  kg may be prescribed unboosted atazanavir if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). However, in order to achieve target drug concentrations, adolescents may require doses of atazanavir that are higher than those recommended for use in adults (see Pediatric Use).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend use of unboosted atazanavir.

### Adolescent and Adult Dose

#### Treatment-Naive Patients:

- Atazanavir/ritonavir (ATV/r) 300 mg/100 mg once daily with food.<sup>d</sup>
- Atazanavir/cobicistat (ATV/c) is currently not approved by the FDA for use in children or adolescents aged <18 years.
- Atazanavir 400 mg once daily with food. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see Pediatric Use).
- Emtricitabine/TAF is approved for use with ATV/r in patients weighing  $\geq 35$  kg.

#### Treatment-Experienced Patients:

- ATV/r 300 mg/100 mg once daily with food.<sup>d</sup>
- ATV/c<sup>e</sup> 300 mg/150 mg once daily with food, or coformulated Evotaz once daily with food.
- ATV/c is currently not approved by the FDA

pump inhibitors. ART-naive patients who are receiving proton-pump inhibitors should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before taking boosted atazanavir. Coadministration of atazanavir with proton-pump inhibitors is not recommended in ART-experienced patients.

- Patients with hepatitis B virus or hepatitis C virus infections and patients who had marked elevations in transaminases before treatment may have an increased risk of further elevations in transaminases or hepatic decompensation.
- Atazanavir oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.

### Powder Administration:

- Mix atazanavir oral powder with at least 1 tablespoon of soft food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup. For young infants (aged <6 months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and given using an oral dosing syringe.
- Administer ritonavir immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

### Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronyl transferase 1A1.

### Atazanavir Dosing in Patients with Hepatic Impairment:

- Atazanavir should be used with caution in patients with mild or moderate hepatic impairment. Consult the manufacturer's prescribing information for the dose adjustment in patients with moderate impairment.
- Atazanavir should not be used in patients with severe hepatic impairment.

for use in children aged <18 years.

- Emtricitabine/TAF is approved for use with ATV/r in patients who weigh  $\geq 35$  kg.

#### **[Evotaz] Atazanavir/Cobicistat**

##### *Child and Adolescent Dose:*

- **ATV/c is currently not approved by the FDA for use in children aged <18 years.**

##### *Adult Dose:*

- **One tablet once daily with food**

#### **Atazanavir Dosing in Patients with Renal Impairment:**

- No dose adjustment is required for patients with renal impairment.
- Atazanavir should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

<sup>a</sup> The mg/kg dosing is higher for the powder packets than for the capsules. In P1020A, children of similar age and size taking atazanavir powder had lower exposures compared with those taking atazanavir capsules.

<sup>b</sup> Children who weigh  $\geq 25$  kg and who cannot swallow atazanavir capsules may receive atazanavir 300 mg (six packets) oral powder plus ritonavir 100 mg oral solution, both administered once daily with food.

<sup>c</sup> Either ritonavir capsules or ritonavir oral solution can be used.

<sup>d</sup> Adult patients who cannot swallow capsules may take atazanavir oral powder once daily with food at the same adult dose as the capsules, along with ritonavir.

<sup>e</sup> See the [cobicistat section](#) for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

## Darunavir (DRV, Prezista) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Oral Suspension:** 100 mg/mL

**Tablets:** 75 mg, 150 mg, 600 mg, 800 mg

**Fixed-Dose Combination Tablets:**

- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg

### Dosing Recommendations

**Note:** Darunavir should not be used without a pharmacokinetic (PK) enhancer (boosting agent). Ritonavir may be used as the boosting agent in children and adults; cobicistat should only be used in adults.

#### Neonate/Infant Dose:

- Darunavir is not approved for use in neonates/infants.

#### Child Dose

*Aged <3 Years:*

- **Do not use darunavir in children aged <3 years or weighing  $\leq 10$  kg.** Seizures and death have been observed in infant rats who received darunavir, and these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

*Aged  $\geq 3$  Years to <12 Years:*

- Dosing recommendations in the table below are for children aged  $\geq 3$  years to <12 years and weighing  $\geq 10$  kg who are treatment-naïve or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with darunavir resistance.

### Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headache
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

### Special Instructions

- Once-daily darunavir is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data and there is limited clinical experience with this dosing schedule in this age group.
- Once-daily darunavir **should not be used** if any one of the following resistance-associated substitutions is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.
- Darunavir must be administered with food, which increases darunavir plasma concentrations by 30%.
- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergies.
- Pediatric dosing requires coadministration of tablets with different strengths to achieve the recommended doses for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.
- Store darunavir tablets and oral suspension at room temperature (25°C or 77°F). Suspension

**Twice Daily Darunavir and Ritonavir Doses for Children Aged 3 Years to <12 Years and Weighing ≥10 kg**

Weight	Dose (Twice Daily with Food) <sup>a</sup>
10 kg to <11 kg <sup>b</sup>	Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 kg to <12 kg <sup>b</sup>	Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL) <sup>c</sup>
12 kg to <13 kg <sup>b</sup>	Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL) <sup>c</sup>
13 kg to <14 kg <sup>b</sup>	Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL) <sup>c</sup>
14 kg to <15 kg	Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL) <sup>c</sup>
15 kg to <30 kg	Darunavir 375 mg (combination of tablets or 3.8 mL <sup>d</sup> ) plus ritonavir 48 mg (0.6 mL <sup>d</sup> )
30 kg to <40 kg	Darunavir 450 mg (combination of tablets or 4.6 mL <sup>d,e</sup> ) plus ritonavir (100 mg tablet or powder or 1.25 mL <sup>b</sup> )
≥40 kg	Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PKs, efficacy, and safety of darunavir/cobicistat is currently under investigation in children aged 12 years to 18 years.

**Child and Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With Darunavir Resistance:**

- Darunavir 450 mg (using a combination of tablets) plus ritonavir 100 mg, both **twice daily with food**

**Child and Adolescent (Aged ≥12 years and Weighing ≥40 kg)<sup>e</sup> and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated With Darunavir Resistance:**

- Darunavir 800 mg (using a tablet or combination of tablets) plus ritonavir 100 mg **once daily with food**

**Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:**

- Darunavir 800 mg (tablet) plus cobicistat<sup>f</sup> 150 mg (tablet) or the coformulation Prezcoibix **once daily with food**

must be shaken well before dosing.

- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor.

**Darunavir Dosing in Patients with Hepatic Impairment:**

- Darunavir is primarily metabolized by the liver. Caution should be used when administering darunavir to patients with hepatic impairment. Darunavir is not recommended in patients with severe hepatic impairment.

**Darunavir Dosing in Patients with Renal Impairment:**

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30–60 mL/min).

**Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir Resistance:**

- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat **is not recommended** with darunavir 600 mg twice daily.

**[Prezcobix] Darunavir/Cobicistat**

*Child and Adolescent (Aged <18 Years) Dose:*

- Prezcobix has not been approved by the Food and Drug Administration (FDA) for use in patients aged <18 years.

*Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:*

- One tablet once daily with food.

**[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Aged <18 Years) Dose:*

- Symtuza has not been approved by the FDA for use in patients aged <18 years.

*Adult Dose:*

- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

<sup>a</sup> Once-daily dosing of darunavir is approved by the FDA, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not **generally** recommend using this dosing schedule in children (see Frequency of Administration below).

<sup>b</sup> Note that the dose in children weighing 10 kg to 15 kg is darunavir 20 mg/kg plus ritonavir 3 mg/kg of body weight per dose, which is higher than the weight-adjusted dose in children with higher weights.

<sup>c</sup> Ritonavir 80 mg/mL oral solution.

<sup>d</sup> The volumes for the 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

<sup>e</sup> Some Panel members recommend the FDA-approved dose of once-daily darunavir 675 mg (administered using a combination of tablets) plus ritonavir 100 mg once daily for adolescents weighing  $\geq 30$  kg to <40 kg (see Table B below).

<sup>f</sup> See the [cobicistat](#) section for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

## Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

#### Oral Solution:

- [Kaletra] Lopinavir 80 mg/mL and ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

#### Film-Coated Tablets:

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

### Dosing Recommendations

#### Neonatal (Aged <14 Days) Dose:

- There are no data on the appropriate dose of lopinavir/ritonavir (LPV/r) for neonates and no data on the safety of using this drug combination in this age group. **Do not administer** LPV/r to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days due to the risk of toxicities.

#### Dosing for Individuals Who Are Not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

##### Infant (Aged 14 Days–12 Months) Dose:

- Once-daily dosing **is not recommended**.
- LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. **Note:** Use of this dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m<sup>2</sup> dose.

##### Child and Adolescent Dose (Aged >12 Months to 18 Years):

- Once-daily dosing **is not recommended**.
- LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥15 kg to 45 kg, this dose

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, alteration of taste
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and Torsades de Pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).

### Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets.**
- LPV/r oral solution should be administered with food, because a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- LPV/r oral solution can be kept at room temperature (up to 77°F or 25°C) if used within 2 months. If kept refrigerated (36°F to 46°F or 2°C to 8°C), LPV/r oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing is not recommended because of considerable variability in plasma

approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

- LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose **should not be used** in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

#### Weight-Band Dosing for Lopinavir 100 mg/Ritonavir 25 mg Pediatric Tablets in Children and Adolescents

	Recommended Number of LPV/r 100 mg/ 25 mg Tablets Given Twice Daily	
<b>Dosing Target</b>	300 mg/m <sup>2</sup> /dose given twice daily	230 mg/m <sup>2</sup> /dose given twice daily
<b>Body Weight</b>		
15 kg to 20 kg	2	2
>20 kg to 25 kg	3	2
>25 kg to 30 kg	3	3
>30 kg to 35 kg	4 <sup>a</sup>	3
>35 kg to 45 kg	4 <sup>a</sup>	4 <sup>a</sup>
>45 kg	4 <sup>a</sup> or 5 <sup>b</sup>	4 <sup>a</sup>

<sup>a</sup> Two tablets that each contain LPV/r 200 mg/50 mg can be substituted for the four LPV/r 100 mg/25 mg tablets in children who are capable of swallowing a larger tablet.

<sup>b</sup> In patients who weigh >45 kg and who are receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, the Food and Drug Administration (FDA)-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

#### Adult (Aged >18 Years) Dose:

- LPV/r 800 mg/200 mg once daily, *or*
- LPV/r 400 mg/100 mg twice daily
- **Do not use** once-daily dosing in children; adolescents; in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir; or in patients with three or more lopinavir-associated

concentrations in children aged <18 years and a higher incidence of diarrhea.

- Use of LPV/r once daily is **contraindicated** if three or more of the following lopinavir resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher lopinavir trough concentrations may be required to suppress resistant virus.

#### Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor.

#### LPV/r Dosing in Patients with Hepatic Impairment:

- LPV/r is primarily metabolized by the liver. Use caution when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.



mutations (see Special Instructions for a list of mutations).

**Dosing for Individuals with Three or More Lopinavir-Associated Mutations (See Special Instructions for List):**

- LPV/r 400 mg/100 mg twice daily

**Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:**

- **Note:** These drugs induce lopinavir metabolism and reduce lopinavir plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing **should not be used** in these patients.

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

*Adult (Aged >18 Years) Dose:*

- The FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing **should not be used**.

**LPV/r Used in Combination with Maraviroc:**

- Maraviroc doses may need modification (see the [maraviroc](#) section for more information).

## Entry and Fusion Inhibitors

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

## Ibalizumab (IBA, Trogarzo) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Single-Dose Vial for Intravenous Administration:** 200 mg/1.33 mL (150 mg/mL) in a single-dose vial

### Dosing Recommendations

#### Child and Adolescent Dose:

- The safety and efficacy of using ibalizumab in children and adolescents has not been established.

#### Adult Dose:

- A single loading dose infusion of 2,000 mg administered intravenously (IV) over 30 minutes is followed by a maintenance dose of 800 mg administered IV over 15 minutes every 2 weeks.
- Food and Drug Administration approval is limited to heavily treatment-experienced adults with multidrug-resistant HIV infection who are experiencing treatment failure on their current regimen.
- Ibalizumab is used in combination with other antiretroviral drugs.

### Selected Adverse Events

- Diarrhea, dizziness, nausea, rash
- Immune reconstitution inflammatory syndrome
- Potential for immunogenicity in the form of anti-ibalizumab antibodies

### Special Instructions

- Using aseptic technique, withdraw 1.33 mL from each vial and transfer into a 250 mL bag of 0.9% sodium chloride for IV injection. Other IV diluents must not be used.
- Once diluted, the solution should be administered immediately. If not used immediately, the solution can be stored at room temperature for up to 4 hours or refrigerated for up to 24 hours. Refrigerated solution should be allowed to stand at room temperature for at least 30 minutes but no more than 4 hours prior to administration.
- Diluted solution is administered as an IV infusion, not as a bolus or IV push.

### Metabolism/Elimination

- Monoclonal antibodies are metabolized to peptides and amino acids

# Maraviroc (MVC, Selzentry) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

## Formulations

**Tablets:** 25 mg, 75 mg, 150 mg, and 300 mg

**Oral Solution:** 20 mg/mL

### Dosing Recommendations

#### Neonate and Infant Dose:

- Maraviroc is not approved by the Food and Drug Administration (FDA) for use in neonates or infants.

#### Pediatric Dose:

- Maraviroc is approved by the FDA for use in treatment-experienced children aged  $\geq 2$  years and weighing  $\geq 10$  kg

#### Recommended Maraviroc Dose for Treatment-Experienced Children Aged $\geq 2$ Years and Weighing $\geq 10$ kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when maraviroc is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs) except tipranavir/ritonavir (TPV/r)			
10 kg to <20 kg	50 mg	2.5 mL	Two 25-mg tablets
20 kg to <30 kg	75 mg to 80 mg	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
$\geq 40$ kg	150 mg	7.5 mL	One 150-mg tablet
Recommended doses when maraviroc is given with non-interacting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine, enfuvirtide, TPV/r, raltegravir			
10 kg to <20 kg	<b>Not recommended.</b> Data are insufficient to make dosing recommendations for children weighing <30 kg and receiving non-interacting medications.		
20 kg to <30 kg	<b>Not recommended.</b> Data are insufficient to make dosing recommendations.		
30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
$\geq 40$ kg	300 mg	15 mL	One 300-mg tablet
Recommended doses when maraviroc is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz and etravirine			
Children in all weight bands	<b>Not recommended.</b> Data are insufficient to make dosing recommendations.		

### Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

### Special Instructions

- Maraviroc is recommended for use in patients who only have CCR5-tropic HIV-1. Conduct testing with a HIV tropism assay (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)) before using maraviroc to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use maraviroc if CXCR4-tropic or mixed/dual-tropic HIV is present.
- Maraviroc can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering maraviroc to patients with underlying cardiac disease.

### Metabolism/Elimination

- Maraviroc is a substrate of CYP3A4. **If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of maraviroc should be adjusted accordingly.**

### Recommended Maraviroc Dose for Adults: Tablets

When Coadministered With:	Dose
Potent CYP3A inhibitors (with or without a potent CYP3A inducer), including all PIs except TPV/r	150 mg twice daily
Non-interacting concomitant medications, including NRTIs, enfuvirtide, TPV/r, nevirapine, raltegravir	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz and etravirine	600 mg twice daily

### Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering maraviroc to patients with hepatic impairment; maraviroc concentrations may be increased in these patients.

### Maraviroc Dosing in Patients with Renal Impairment:

- There are no data to recommend specific doses of maraviroc in pediatric patients with mild or moderate renal impairment. Maraviroc is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease on regular hemodialysis who are receiving potent CYP3A inhibitors.
- Refer to the manufacturer's prescribing information for the appropriate doses to use in adult patients with renal impairment.

## **Integrase Inhibitors**

Bictegravir (BIC)

Dolutegravir (DTG, Tivicay)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

## Bictegravir (BIC) (Last updated September 12, 2019; last reviewed September 12, 2019)

For additional information, see Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Note:** Bictegravir is only available in a fixed-dose combination tablet (FDC).

#### Fixed-Dose Combination Tablet:

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg

When using FDC tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

### Dosing Recommendations

#### [Biktarvy] Bictegravir/Emtricitabine/TAF

*Child (Weighing <25 kg) Dose:*

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg. **Studies are currently being conducted to identify the appropriate dose for this age and weight group.**

*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*

- One tablet once daily **with or without food** in antiretroviral (ARV) therapy-naive patients. This dose of Biktarvy can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

### Selected Adverse Events

- Diarrhea, nausea, headache
- See the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for information about the adverse events that are associated with the use of these drugs.

### Special Instructions

- Administer Biktarvy with or without food. See “Drug Interactions” for guidance if administering with antacids or iron or calcium supplements.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine or TAF. Severe acute exacerbation of HBV can occur when discontinuing emtricitabine or TAF; therefore, monitor hepatic function for several months after halting therapy with emtricitabine or TAF.
- Biktarvy **is not recommended** for use with other ARV drugs.

### Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.
- Refer to the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for more information about the metabolism and elimination of these components of Biktarvy.

#### Biktarvy Dosing in Patients with Hepatic Impairment:

- Biktarvy **is not recommended** for use in patients with severe hepatic impairment.

#### Biktarvy Dosing in Patients with Renal Impairment:

- Biktarvy **is not recommended** for use in patients with estimated creatinine clearance <30 mL/min.

## Dolutegravir (DTG, Tivicay) (Last updated September 12, 2019; last reviewed September 12, 2019)

For additional information, see Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Tablets:** 10 mg, 25 mg, and 50 mg

#### Fixed-Dose Combination Tablets:

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for special instructions, drug interaction information, and additional information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

### Dosing Recommendations

#### Neonate and Infant Dose:

- Dolutegravir is not approved for use in neonates/infants.

#### Child (Weighing <20 kg) Dose:

- No dosing recommendations can be made for children weighing <20 kg.

#### Child and Adolescent (Weighing ≥20 kg to <40 kg) Dose:

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends an investigational dose of dolutegravir 50 mg once daily for children and adolescents weighing ≥20 kg who are antiretroviral (ARV)-naïve or ARV-experienced (but integrase strand transfer inhibitor [INSTI]-naïve) and who are not being treated with uridine diphosphate glucuronyl transferase (UGT) 1A1 or cytochrome P450 3A (CYP3A) inducers or inhibitors.
- Dolutegravir is not approved by the Food and Drug Administration (FDA) for use in children weighing <30 kg. However, interim data from ongoing trials that indicate that using the FDA-approved dose of dolutegravir 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations, and additional data supports the 50-mg dose recommended by the Panel (see text). Using a 50-mg dose also avoids the need to administer two tablets with different strengths (i.e., a 10-mg tablet plus a 25-mg tablet).

### Selected Adverse Events

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness
- Rare cases of hypersensitivity reactions, including rash and drug reaction (or rash) with eosinophilia and systemic symptoms, constitutional symptoms, and organ dysfunction (including liver injury) have been reported.

### Special Instructions

- Dolutegravir may be taken without regard to meals.
- Dolutegravir should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.
- In patients who have difficulty swallowing tablets whole, 10-mg, 25-mg, and 50-mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately**.<sup>1</sup>
- The efficacy of dolutegravir 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the [Resistance](#) section below).



### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose

Population	Recommended Dose
ARV-naive or ARV-experienced/ INSTI-naive patients	Dolutegravir 50 mg once daily
ARV-naive or ARV-experienced/ INSTI-naive patients who are also receiving one of the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	Dolutegravir 50 mg twice daily <sup>a</sup>
INSTI-experienced patients with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance <sup>9</sup>	Dolutegravir 50 mg twice daily <sup>a,b</sup>

<sup>a</sup> The 50-mg, twice-daily dose should not be used in patients weighing  $< 40$  kg.

<sup>b</sup> These patients should receive drug combinations that do not include metabolic inducers when possible.

#### [Dovato] Dolutegravir/Lamivudine

##### Adult Dose:

- One tablet once daily with or without food as a complete regimen in ARV-naive adults with no known substitutions associated with resistance to the individual components of Dovato.
- Dovato is not approved for use in children or adolescents. See the Simplification of Treatment section below.

#### [Juluca] Dolutegravir/Rilpivirine

##### Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.
- Juluca is not approved for use in children or adolescents. See the Simplification of Treatment section below.

#### [Triumeq] Abacavir/Dolutegravir/Lamivudine

##### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose:

- One tablet once daily with or without food.
- For use in patients who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1 or CYP3A inducers.
- See the [abacavir section](#) for special instructions about testing for abacavir hypersensitivity.
- The FDA-approved dose for pediatric patients weighing  $\geq 40$  kg is one tablet once daily.

- Patients should be tested for hepatitis B virus (HBV) infection prior to use of Triumeq or Dovato. Lamivudine-resistant HBV variants have been reported in patients who received lamivudine-containing ARV regimens. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection. Severe exacerbation of hepatitis can occur in patients with HBV/HIV coinfection who discontinue lamivudine.

### Metabolism/Elimination

- UGT1A1 and CYP3A substrate: Drugs that induce these enzymes and transporters may decrease plasma concentrations of dolutegravir. Drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

#### Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to a lack of data, dolutegravir is not recommended for use in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and increases measured serum creatinine, without affecting glomerular filtration.

#### Dolutegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients with mild or moderate renal impairment.
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance  $< 30$  mL/min), because dolutegravir concentrations will be decreased. The cause of this decrease is unknown.

## Elvitegravir (EVG) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <https://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Tablet:** Discontinued by the manufacturer. Elvitegravir is only available in fixed-dose combination (FDC) tablets.

#### Fixed-Dose Combination Tablets:

- [*Genvoya*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- [*Stribild*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg

### Dosing Recommendations

#### [*Genvoya*] Elvitegravir/Cobicistat/Emtricitabine/TAF

*Child (Weighing <25 kg) Dose:*

- There are no data on the appropriate dose of elvitegravir in *Genvoya* for children weighing <25 kg.

*Child and Adolescent (Weighing ≥25 kg) and Adult Dose:*

- One tablet once daily **with food**

#### [*Stribild*] Elvitegravir/Cobicistat/Emtricitabine/TDF

*Child and Adolescent (Weighing <35 kg) Dose:*

- There are no data on the appropriate dose of elvitegravir in *Stribild* for children or adolescents weighing <35 kg.

*Adolescent (Weighing ≥35 kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose:*

- One tablet once daily **with food**

**Note:** *Stribild* and *Genvoya* are approved by the Food and Drug Administration for use in antiretroviral (ARV)-naïve patients or to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of *Genvoya* or *Stribild*.

### Selected Adverse Events

#### Elvitegravir-Associated Adverse Events:

- Diarrhea

#### *Stribild*-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

#### *TDF*-Specific Adverse Events:

- **Glomerular and proximal renal tubular dysfunction**
- Decreased bone mineral density
- Flatulence

#### *Cobicistat*-Specific Adverse Events:

- **Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine.**

#### *Genvoya*-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

#### *TAF*-Specific Adverse Events:

- Increased levels of low-density lipoprotein cholesterol and total cholesterol.

#### *Cobicistat*-Specific Adverse Events:

- **Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine.**

## Special Instructions

- Administer both Genvoya and Stribild with food.
- Separate elvitegravir dosing from antacids and iron, calcium, aluminum, and/or magnesium-containing supplements and multivitamins by at least 4 hours.
- When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 months to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels  $>0.4$  mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with emtricitabine, TDF, or TAF.

## Metabolism/Elimination

- Elvitegravir is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- Elvitegravir should only be used with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the TDF and TAF sections for further details.
- Stribild **should not be initiated** in patients with estimated CrCl  $<70$  mL/min, and it should be discontinued in patients with estimated CrCl  $<50$  mL/min. Emtricitabine and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya **should not be initiated** in patients with estimated CrCl  $<30$  mL/min.
- Stribild and Genvoya **should be not used** in patients with severe hepatic impairment.

## Raltegravir (RAL, Isentress) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Tablet:** 400 mg (film-coated poloxamer tablet)

**HD Tablet:** 600 mg (film-coated poloxamer tablet)

**Chewable Tablets:** 100 mg (scored) and 25 mg

**Granules for Oral Suspension:** Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for final concentration of 10 mg/mL.

**Note:** Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

### Dosing Recommendations

**Note:** No dosing information is available for preterm infants or **infants weighing <2 kg at birth**. (See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#) for information about using raltegravir for the prevention of perinatal HIV transmission).

#### Neonate (Weighing $\geq 2$ kg) Dose

**Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks: Neonates Aged  $\geq 37$  Weeks and Weighing  $\geq 2$  kg**

Body Weight	Volume (Dose) of Suspension
<b>Birth to 1 Week of Age: Once-Daily Dosing</b>	<b>Approximately 1.5 mg/kg/dose</b>
2 kg to <3 kg	0.4 mL (4 mg) once daily
3 kg to <4 kg	0.5 mL (5 mg) once daily
4 kg to <5 kg	0.7 mL (7 mg) once daily
<b>1–4 Weeks of Age: Twice-Daily Dosing</b>	<b>Approximately 3 mg/kg/dose</b>
2 kg to <3 kg	0.8 mL (8 mg) twice daily
3 kg to <4 kg	1 mL (10 mg) twice daily
4 kg to <5 kg	1.5 mL (15 mg) twice daily

**Note:** If the mother has taken raltegravir 2 hours to 24 hours prior to delivery, the neonate's first dose should be delayed until 24 hours to 48 hours after birth.

**Note:** Metabolism by uridine diphosphate glucuronyl transferase (UGT1A1) is low at birth and increases rapidly during the next 4 to 6 weeks of life.

#### Infant and Child (Weighing $\geq 3$ kg to <20 kg) Dose

### Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

### Special Instructions

- Raltegravir can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any raltegravir formulations.
- Significant drug interactions are more likely to occur when the raltegravir HD formulation is used once daily. **The following drugs should not be coadministered:** calcium carbonate, rifampin, tipranavir/ritonavir, and etravirine.
- Chewable tablets can be chewed, crushed (before administration), or swallowed whole.
- Film-coated tablets, including HD tablets, must be swallowed whole.
- The chewable tablets and oral suspension have better bioavailability than the film-coated tablets. Because the formulations are not interchangeable, **do not substitute** chewable tablets or oral suspension for film-coated tablets. See specific recommendations for proper dosing of different formulations.

### Raltegravir Oral Suspension Dosing Table for Patients Aged $\geq 4$ Weeks<sup>a</sup>

Body Weight	Volume (Dose) of Suspension to be Administered Twice Daily
3 kg to <4 kg	2.5 mL (25 mg)
4 kg to <6 kg	3 mL (30 mg)
6 kg to <8 kg	4 mL (40 mg)
8 kg to <11 kg	6 mL (60 mg)
11 kg to <14 kg	8 mL (80 mg)
14 kg to <20 kg	10 mL (100 mg)

<sup>a</sup> The weight-based dosing recommendation for the oral suspension is based on approximately raltegravir 6 mg/kg per dose twice daily.

**Note:** The maximum dose of oral suspension is 10 mL (raltegravir 100 mg) twice daily.

**Note:** For children weighing 11 kg to 20 kg, either oral suspension or chewable tablets can be used.

### Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

*Children Weighing  $\geq 11$  kg:*

- Weighing <25 kg: Chewable tablets twice daily. See table below for chewable tablet dose.
- Weighing  $\geq 25$  kg: Raltegravir 400-mg, film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

*Children and Adolescents Weighing  $\geq 50$  kg:*

- Two raltegravir 600-mg HD tablets (1,200 mg) once daily
- This dose is for treatment-naïve or virologically suppressed patients who are on an initial dose of raltegravir 400 mg twice daily.
- See the Approval section under the Pediatric Use heading below for more information.

### Chewable Tablet Dosing Table<sup>a</sup>

Body Weight	Dose	Number of Chewable Tablets
11 kg to <14 kg	Raltegravir 75 mg twice daily	Three 25-mg tablets twice daily
14 kg to <20 kg	Raltegravir 100 mg twice daily	One 100-mg tablet twice daily
20 kg to <28 kg	Raltegravir 150 mg twice daily	One and a half 100-mg tablets <sup>b</sup> twice daily
28 kg to <40 kg	Raltegravir 200 mg twice daily	Two 100-mg tablets twice daily
$\geq 40$ kg	Raltegravir 300 mg twice daily	Three 100-mg tablets twice daily

<sup>a</sup> The weight-based dose recommendation for the chewable tablet is based on approximately raltegravir 6 mg/kg per dose twice daily.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.
- The chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- The oral suspension comes in a kit that includes mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. Each foil packet is single-use and contains 100 mg of raltegravir, which will be suspended in 10 mL of water for a final concentration of raltegravir 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.
- **Do not shake the oral suspension.** Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document.

### Metabolism/Elimination

- UGT1A1-mediated glucuronidation

### Raltegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients who have mild-to-moderate hepatic insufficiency and are receiving twice daily dosing of raltegravir.
- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving either raltegravir 1,200 mg once daily or 400 mg twice daily.
- No studies have been conducted on the use of raltegravir HD in patients with hepatic impairment. Therefore, administration of raltegravir HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on raltegravir pharmacokinetics has not been studied.

### Raltegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with any degree of renal impairment.

<sup>b</sup> The raltegravir 100-mg chewable tablet can be divided into equal halves.

**Note:** Maximum dose of chewable tablets is raltegravir 300 mg twice daily.

## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

## Cobicistat (COBI, Tybost) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Tablet:** 150 mg

#### Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

### Dosing Recommendations

#### Cobicistat is a Pharmacokinetic Enhancer:

- The only use of cobicistat is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase inhibitors. Cobicistat **is not interchangeable** with ritonavir.

#### Use of Cobicistat-Containing Drugs in Children and Adolescents

*Not Food and Drug Administration (FDA)-Approved for Use in Children and Adolescents Aged <18 Years:*

- Cobicistat alone (as Tybost)
- Evotaz
- Prezcobix
- **Symtuza**
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) regard the above agents as potentially appropriate for use in certain children aged <18 years and weighing  $\geq 35$  kg. An expert in pediatric HIV infection should be consulted before using these drugs in these patients. See the [atazanavir](#) and [darunavir](#) sections for additional information.

*FDA-Approved for Use in Children and Adolescents Weighing  $\geq 25$  kg:*

- Genvoya

*FDA-Approved for Use in Children and Adolescents Aged  $\geq 12$  and Weighing  $\geq 35$  kg:*

- Stribild
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

### Selected Adverse Events

- Cobicistat is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function.

### Special Instructions

- Cobicistat 150 mg is **not interchangeable** with ritonavir, but it has a PK boosting effect that is comparable to ritonavir 100 mg.
- Drug interactions may differ between **ritonavir and cobicistat, because cobicistat is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of ritonavir.**
- **Genvoya, Stribild, and Symtuza are approved for use in treatment-naive patients. They can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of these single-tablet regimens.**
- **Do not administer** cobicistat with ritonavir or with FDC tablets that contain cobicistat.
- Not recommended for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Use with PIs other than once-daily atazanavir 300 mg or darunavir 800 mg **is not recommended.**
- Patients with a confirmed increase in serum



## Adult (Aged ≥18 Years) Dose

*Cobicistat Must be Administered as:*

- The fixed-dose combination (FDC) tablets Stribild, Genvoya, or **Symtuza**, which are complete regimens and should not be administered with any other antiretroviral (ARV) drugs; *or*
  - The tablet Tybost, which should be administered at the same time as atazanavir or darunavir at the doses listed in the table below and used in combination with other ARV drugs; *or*
  - The FDC tablets Evotaz (which also contains atazanavir) or Prezcofix (which also contains darunavir). Both FDC tablets should be administered with food and in combination with other ARV drugs.
- When using cobicistat in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 months to 6 months while the patient is receiving therapy (see [Table 15i](#)). In patients who are at risk of renal impairment, serum phosphate should also be monitored.
  - When using cobicistat in combination with other ARV drugs, or when using FDC tablets that contain cobicistat, see other drug sections for special instructions and additional information about the individual drug components (e.g., [atazanavir](#), [darunavir](#), [elvitegravir](#), [TDF](#), [TAF](#)).

### Doses for Cobicistat and Coadministered Antiretroviral Drugs

Cobicistat Dose	Coadministered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild, Genvoya, or <b>Symtuza</b>	Treatment-naïve or treatment-experienced, with virus that is susceptible to all ARV drug components of Stribild, Genvoya, or <b>Symtuza</b>
150 mg orally once daily	Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) given orally once daily	Treatment-naïve or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (coformulated as Prezcofix or given as a separate drug) given orally once daily	Treatment-naïve or treatment-experienced, with no darunavir-associated resistance mutations

## Metabolism/Elimination

- Cobicistat is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

### Cobicistat Dosing in Patients with Renal Impairment:

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl) <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min. The dose adjustments required for emtricitabine and TDF in these patients cannot be achieved with an FDC tablet.
- Neither Genvoya nor **Symtuza** should be initiated in patients with estimated CrCl <30 mL/min.
- Stribild, Genvoya, and **Symtuza** should not be used in patients with severe hepatic impairment.

## Ritonavir (RTV, Norvir) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Oral Powder:** 100 mg per packet

**Oral Solution:** 80 mg/mL. Oral solution contains 43% (v/v) ethanol and approximately 27% (w/v) propylene glycol.

**Tablets:** 100 mg

### Generic Formulation

**Tablets:** 100 mg

### Fixed-Dose Combination Solution:

- [Kaletra] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.

### Fixed-Dose Combination Tablets:

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

### Dosing Recommendations

#### Ritonavir as a Pharmacokinetic Enhancer:<sup>a</sup>

- Ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See other sections of the [Drug Appendix](#) for information about the recommended doses of ritonavir to use with specific PIs.

#### Formulation Considerations:

- The oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- Ritonavir oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

#### [Kaletra] Lopinavir/Ritonavir

##### Infant, Child, Adolescent, and Adult Dose:

- See the [Lopinavir/Ritonavir](#) section of the [Drug Appendix](#).

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Hyperglycemia
- Fat maldistribution

### Special Instructions

- Administer ritonavir with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).
- **Do not refrigerate** ritonavir oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- Ritonavir oral powder should be mixed with a soft food (e.g., apple sauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste. Administer or discard the mixture within 2 hours of mixing.

### **To Increase Tolerability of Ritonavir Oral Solution in Children:**

- Mix the solution with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering ritonavir, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a child peanut butter to coat the mouth.
- After administration, give strong-tasting foods (e.g., maple syrup, cheese).
- Check a child's food allergy history before making these recommendations.
- Counsel parents or patients that the bad taste will not be completely masked.

### **Metabolism/Elimination**

- Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.  
**Ritonavir inhibits the intestinal transporter P-glycoprotein.**

### **Ritonavir Dosing in Patients with Hepatic Impairment:**

- Ritonavir is primarily metabolized by the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.

<sup>a</sup> Ritonavir has antiviral activity, but it is not used as an antiviral agent (see text).

## Archived Drugs

### *Overview*

The Archived Drugs section of Appendix A: Pediatric Antiretroviral Drug Information provides access to the last updated versions of drug sections that are no longer being reviewed by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel). Archived Drugs includes older antiretroviral drugs that the Panel does not recommend for use in children because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data.

Didanosine

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

## Didanosine (ddl, Videx) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Pediatric Oral Solution:** 10 mg/mL

**Enteric-Coated (EC) Delayed-Release Capsules (EC Beadlets):** 125 mg, 200 mg, 250 mg, and 400 mg

### Generic Formulations

**Delayed-Release Capsules:** 125 mg, 200 mg, 250 mg, and 400 mg

### Dosing Recommendations

**Note:** Didanosine **is no longer recommended** by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV for use in children due to higher rates of adverse effects than other NRTIs.

#### Neonate/Infant Dose (Aged 2 Weeks to <3 Months):

- 50 mg/m<sup>2</sup> of body surface area every 12 hours. See dosing section below for justification of this dose.

#### Infant Dose (Aged ≥3 Months to 8 Months):

- 100 mg/m<sup>2</sup> body surface area every 12 hours

#### Pediatric Dose of Oral Solution (Age >8 Months):

- 120 mg/m<sup>2</sup> body surface area every 12 hours
- Dose range: 90–150 mg/m<sup>2</sup> body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naïve children ages 3 years to 21 years, 240 mg/m<sup>2</sup> body surface area once daily (oral solution or capsules) has resulted in viral suppression.

#### Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥20 kg)

Body Weight	Dose
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

#### Adolescent and Adult Dose

Body Weight	Dose
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

### Selected Adverse Events

- Peripheral neuropathy
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (the risk is increased when didanosine is used in combination with stavudine).
- Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir disoproxil fumarate or stavudine)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

### Special Instructions

- Administer didanosine on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).
- Didanosine powder for oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration.
- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.

### Metabolism/Elimination

- Renal excretion 50%

**Pediatric and Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate:**

- This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic nonresponse, high rates of early virologic failure, and rapid selection of resistance mutations (see the [Adult and Adolescent Guidelines](#)).
- Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

## Enfuvirtide (T-20, Fuzeon) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

#### Lyophilized Powder for Injection:

- 108-mg vial of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

#### Convenience Kit:

- 60 single-use vials of enfuvirtide (108-mg vial reconstituted as 90 mg/mL), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes.

### Dosing Recommendations

#### Pediatric and Adolescent Dose (Aged 6–16 Years)

##### Children Aged <6 Years:

- Not approved for use in children aged <6 years

##### Children Aged ≥6 Years:

- 2 mg/kg (maximum dose 90 mg [1 mL]) twice daily injected subcutaneously (SQ) into the upper arm, anterior thigh, or abdomen

#### Adolescent (Aged >16 Years) and Adult Dose:

- 90 mg (1 mL) twice daily injected SQ into the upper arm, anterior thigh, or abdomen

### Selected Adverse Events

- Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in up to 98% of patients.
- Increased rate of bacterial pneumonia (unclear association).
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

### Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of SQ injections. Enfuvirtide injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject enfuvirtide immediately or keep refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours.
- Enfuvirtide must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions, apply ice or heat after injection or gently massage injection

site to better disperse the dose. There are reports of injection-associated neuralgia and paresthesia when alternative delivery systems, such as needle-free injection devices, are used.

- Advise patients/caregivers of the possibility of a HSR; instruct them to discontinue treatment and seek immediate medical attention if a patient develops signs and symptoms consistent with a HSR.

### **Metabolism/Elimination**

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- Catabolism to constituent amino acids.



## Fosamprenavir (FPV, Lexiva) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Tablets:** 700 mg

**Oral Suspension:** 50 mg/mL

### Dosing Recommendations

#### Pediatric Dose (Aged >6 Months to 18 Years):

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants  $\geq 4$  weeks and for treatment-experienced infants  $\geq 6$  months; however, the Panel does not recommend use in infants aged <6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks' gestation or greater.

**Note:** Once-daily dosing **is not recommended** for any pediatric patient.

#### Pediatric Dose (Aged $\geq 6$ Months to 18 Years):

#### Twice-Daily Dose Regimens by Weight for Pediatric Patients $\geq 6$ Months Using Fosamprenavir Oral Suspension with Ritonavir

Weight	Dose (Both Drugs Twice Daily <sup>a</sup> with Food)
<11 kg	Fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose
11 kg to <15 kg	Fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose
15 kg to <20 kg	Fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose
$\geq 20$ kg	Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose

<sup>a</sup> Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

### Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

### Special Instructions

- Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.
- Patients taking antacids should take fosamprenavir at least 1 hour before or after antacid use.
- Fosamprenavir contains a sulfonamide moiety. The potential for cross sensitivity between fosamprenavir and other drugs in the sulfonamide class is unknown. Fosamprenavir should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

### Metabolism/Elimination

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P (CYP) 450 3A4 inhibitor, inducer, and substrate.

**Note:** When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing  $\geq 39$  kg. Ritonavir tablets can be used in patients weighing  $\geq 33$  kg.

**Adolescent and Adult Dose:**

- Dosing regimen depends on whether the patient is ARV-naive or ARV-experienced.

*ARV-Naive Patients*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily
- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily

*Protease-Inhibitor-Experienced Patients:*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily

**Note:** Once-daily administration of fosamprenavir plus ritonavir **is not recommended**.

**Fosamprenavir Dosing in Patients with Hepatic Impairment:**

- Specific dose adjustments are recommended for adults with mild, moderate, and severe hepatic impairment. However, there are no data to support dosing recommendations for pediatric patients with hepatic impairment. Please refer to the package insert.

**Fosamprenavir Dosing in Patients with Renal Impairment:**

- No dose adjustment is required in patients with renal impairment.

## Indinavir (IDV, Crixivan) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Capsules:** 100 mg, 200 mg, and 400 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Not approved for use in neonates/infants
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus)

#### Pediatric Dose:

- Not approved for use in children
- A range of indinavir doses (234–500 mg/m<sup>2</sup> body surface area) boosted with low-dose ritonavir has been studied in children (see text below).

#### Adolescent and Adult Dose:

- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of indinavir in adolescents.

### Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

### Special Instructions

- When indinavir is given in combination with ritonavir, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis ( $\geq 48$  oz of fluid daily in adult patients).
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate

#### Indinavir Dosing in Patients with Hepatic Impairment:

- Dose should be decreased in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

## Nelfinavir (NFV, Viracept) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

Tablets: 250 mg and 625 mg

#### Dosing Recommendations

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **no longer recommends** nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

##### Neonate and Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

##### Pediatric Dose (Aged $\geq 2$ Years):

- 45–55 mg/kg twice daily

##### Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily

#### Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Serum transaminase elevations

#### Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

#### Metabolism/Elimination

- Cytochrome P (CYP) 2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

## Saquinavir (SQV, Invirase) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf>

### Formulations

**Capsules:** 200 mg

**Tablets:** 500 mg

### Dosing Recommendations

#### Pediatric Dose:

- Not approved for use in infants, children, and adolescents aged <16 years.

#### Adolescent and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg twice daily

### Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)

### Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended; saquinavir is **contraindicated** in patients with a prolonged QT interval.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor
- 90% metabolized in the liver
- Use saquinavir with caution in patients who have hepatic impairment; no dose adjustment recommended.

## Stavudine (d4T, Zerit) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Powder for Oral Solution:** 1 mg/mL

**Capsules:** 15 mg, 20 mg, 30 mg, and 40 mg

#### Generic Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

### Dosing Recommendations

**Note:** Stavudine **is no longer recommended** for use in children by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, because it causes higher rates of adverse effects than other nucleoside reverse transcriptase inhibitors (NRTIs).

#### Pediatric (Aged $\geq 14$ Days and Weighing $< 30$ kg)

##### Dose:

- 1 mg/kg per dose twice daily

#### Adolescent (Weighing $\geq 30$ kg) and Adult Dose:

- 30 mg per dose twice daily

### Selected Adverse Events

- Associated with a higher risk of mitochondrial toxicity than other NRTI drugs
- Peripheral neuropathy is dose-related and occurs more frequently in patients who have advanced HIV disease or a prior history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy.
- Facial/peripheral lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other NRTIs). The risk increases when stavudine is used in combination with didanosine.
- Dyslipidemia
- Insulin resistance, asymptomatic hyperglycemia
- Rapidly progressive ascending neuromuscular weakness (rare)

### Special Instructions

- Stavudine can be given without regard to food.
- Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.

### Metabolism/Elimination

- Renal excretion 50%. Decrease dose in renal dysfunction.
- Stavudine is phosphorylated intracellularly to the active metabolite stavudine triphosphate.

## Tipranavir (TPV, Aptivus) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Oral Solution:** 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL

**Capsules:** 250 mg

### Dosing Recommendations

**Note:** Tipranavir must be boosted with ritonavir. The ritonavir boosting dose used for tipranavir is higher than the doses used for other protease inhibitors.

#### Pediatric (Aged <2 Years) Dose:

- Not approved for use in children aged <2 years

#### Pediatric (Aged 2–18 Years) Dose:

**Note:** Not recommended for treatment-naïve patients

#### Body Surface Area Dosing:

- Tipranavir/ritonavir (TPV/r) 375 mg/m<sup>2</sup>/150 mg/m<sup>2</sup>, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)

#### Weight-Based Dosing:

- TPV/r 14 mg/kg/6 mg/kg, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)

#### Adult Dose:

- TPV/r 500 mg (as two 250-mg capsules)/200 mg, both twice daily
- **Note:** Not recommended for treatment-naïve patients

### Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash (more common in children than adults)
- Nausea, vomiting, diarrhea
- Hepatotoxicity: elevated transaminases; clinical hepatitis
- Hyperlipidemia
- Hyperglycemia
- Elevated creatine phosphokinase

### Special Instructions

- Administer tipranavir and ritonavir together and with food.
- Tipranavir oral solution contains 116 IU vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- Store tipranavir oral solution at room temperature, 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store unopened bottles of oral tipranavir capsules in a refrigerator at 2°C to 8°C (36°F to 46°F). Once the bottle has been opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.
- Use tipranavir with caution in patients who may be at increased risk of intracranial hemorrhage, including individuals with brain

lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcoholism, or who use anticoagulant or antiplatelet agents (including vitamin E).

- Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.

### **Metabolism/Elimination**

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate
- P-glycoprotein substrate

#### Tipranavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required.

#### Tipranavir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required for mild hepatic impairment.
- Use of tipranavir is **contraindicated** in patients with moderate-to-severe hepatic impairment.