



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

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## **Appendix A: Pediatric Antiretroviral Drug Information**

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

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Stavudine (d4T, Zerit)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

## Abacavir (ABC, Ziagen) (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:** 300 mg (scored)

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

**Fixed-Dose Combination Tablets:**

- [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
- [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

**Generic Formulations:**

- Abacavir sulfate 300 mg tablets
- Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg
- Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

### Dosing Recommendations

**Neonate/Infant Dose:**

- Not approved for infants aged <3 months.

**Pediatric Dose**

*Oral Solution (Aged ≥3 Months):*

- 8 mg/kg (maximum 300 mg per dose) twice daily or 16 mg/kg once daily (maximum 600 mg per dose) (see text below).
- In infants and young children being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) cell count/percentage for more than 6 months (24 weeks) on liquid formulation of abacavir twice daily, dose can be changed from twice daily to once daily with liquid or tablet formulations (see text below).

**Weight Band Dosing (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)	1 ½ tablets (450 mg)
≥25 kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

### Selected Adverse Events

- Hypersensitivity reactions (HSR) 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 and shortness of breath).

### Special Instructions

- Test patients for the HLA-B\*5701 allele before starting therapy to predict risk of HSR. Patients 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 risk of serious, potentially fatal HSRs. Occurrence of HSRs requires **immediate and permanent discontinuation** of abacavir. **Do not re-challenge.**
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.
- **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.**

- In patients who can be treated with pill formulations, therapy can be initiated with once-daily administration.

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

- 300 mg twice daily or 600 mg once daily.

**[Trizivir] Abacavir plus Lamivudine plus Zidovudine**

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

- One tablet twice daily.

**[Epzicom] Abacavir plus Lamivudine**

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

- One tablet once daily.

**[Triumeq] Abacavir plus Dolutedgravir plus Lamivudine**

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

- One tablet once daily.

- For use in patients who are antiretroviral (ARV) treatment-naïve or treatment-experienced (but INSTI-naïve) and not being treated with UGT1A1/CYP3A inducers.

**Metabolism/Elimination**

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Active metabolite is 82% renally excreted.
- Abacavir requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents), in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents) in patients with creatinine clearance  $< 50$  mL/min and patients on dialysis (because of the fixed dose of lamivudine).

# 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.

## Emtricitabine (FTC, Emtriva) (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

**Capsules:** 200 mg

**Fixed-Dose Combination Tablets:**

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

### Dosing Recommendations

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

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

*Oral Solution:*

- 3 mg/kg once daily

#### Pediatric (Aged ≥3 Months to 17 Years) Dose

*Oral Solution:*

- 6 mg/kg (to a maximum dose of 240 mg) once daily; the maximum dose of oral solution is higher than the capsule dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.

*Capsules (Patients Weighing >33 kg):*

- 200 mg once daily

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

*Oral Solution for Those Unable to Swallow*

*Capsules:*

- 240 mg (24 mL) once daily

*Capsules:*

- 200 mg once daily

### Selected Adverse Events

- Severe acute exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV 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 fixed-dose combination (FDC) tablet **formulations** that contain emtricitabine.
- **When using FDC tablets, see other sections of the [drug appendix](#) for special instructions and additional information about the individual components of the FDC.**
- Emtricitabine oral solution can be kept at room temperature, up to 77°F (25°C), if used within 3 months; refrigerate for longer-term storage.
- Before using emtricitabine, screen patients for HBV

### Metabolism/Elimination

- No cytochrome P (CYP) 450 interactions
- Renal excretion of emtricitabine is 86%.

### [Truvada] Emtricitabine plus TDF (FTC/TDF)

*Pediatric Dose:*

#### Truvada Pediatric 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	One FTC/TDF 200 mg/300 mg tablet

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

- 1 FTC/TDF 200 mg/300 mg tablet once daily

### [Descovy] Emtricitabine plus TAF

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

- *Body Weight 25 to <35 kg:* 1 tablet once daily in combination with other antiretroviral (ARV) agents, except for protease inhibitors (PIs) that require a CYP3A inhibitor (i.e., emtricitabine/TAF [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 ≥35 kg:* 1 tablet once daily in combination with an INSTI, NNRTI, or boosted PI

### [Atripla] Efavirenz plus Emtricitabine plus TDF

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

- 1 tablet once daily
- Administer without food.

### [Complera] Emtricitabine plus Rilpivirine plus TDF

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

- 1 tablet once daily in antiretroviral treatment (ART)-naïve patients who have baseline plasma HIV-1 RNA <100,000 copies/mL. This Complera dose 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-1 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.

Emtricitabine may compete with other compounds that undergo renal elimination.

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

- Decrease dose in patients with impaired renal function. Consult manufacturer's prescribing information.
- 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. Increase monitoring 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 patients with estimated CrCl <30 mL/min.



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

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

- 1 tablet once daily as initial therapy in ART-naive patients with HIV-1 RNA  $\leq 100,000$  copies per mL. This Odefsey dose can also be used to replace a stable ART regimen in patients who have been virologically suppressed (HIV-1 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 plus Cobicistat plus Emtricitabine plus TDF**

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

- 1 tablet once daily **with food** in ART-naive patients. This Stribild dose can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 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.

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

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

- 1 tablet once daily with food in ART-naive patients. This Genvoya dose can also be used to replace the current ART regimen in patients who have been virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) on a stable ART 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.

### **[Biktarvy] Bictegravir plus Emtricitabine plus TAF**

*Pediatric and Adolescent Dose (Aged  $< 18$  Years):*

- Biktarvy has not been Food and Drug Administration-approved for use in patients aged  $< 18$  years.
- *Children aged  $< 12$  years:* No data on appropriate dose of Biktarvy in children aged  $< 12$  years
- *Children and adolescents (aged  $\geq 12$  to 18 years and weighing  $\geq 35$  kg):* 1 tablet once

daily. This is an **investigational dose.**

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

- 1 tablet once daily in ART-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA  $<50$  copies/mL) on a stable ARV regimen for at least 3 months 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.

## Lamivudine (3TC, Epivir) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

#### Pediatric Oral Solution:

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

#### Tablets:

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

#### Generic Formulations:

Tablets: 100 mg, 150 mg, and 300 mg

#### Fixed-Dose Combination Tablets:

- [Combivir and Generic] Lamivudine 150 mg plus zidovudine 300 mg
- [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
- [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

### Dosing Recommendations

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

#### Neonate ( $\geq 32$ Weeks Gestation at Birth) and Infant (Birth to $< 4$ Weeks) Treatment Dose:

- 2 mg/kg twice daily (oral solution)

#### Pediatric 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 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:

- 4 mg/kg twice daily of the oral solution

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

- 5 mg/kg twice daily of the oral solution, up to 150 mg

#### Aged $\geq 3$ Years:

- 5 mg/kg twice daily of the oral solution, up to

### Selected Adverse Events

- Exacerbation of hepatitis has been reported after discontinuation of lamivudine in the setting of chronic hepatitis B virus (HBV) infection.

### 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.
- When using fixed-dose combinations, see other drug sections for special instructions and additional information about the individual drug components.

### Metabolism/Elimination

- Dose adjustment required in patients with renal insufficiency.
- Fixed-dose combination tablets should not be used in patients who are on dialysis or who have creatinine clearance  $< 50$  mL/min or impaired hepatic function.

150 mg; *or*

- 10 mg/kg once daily of the oral solution, up to 300 mg

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

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

**Weight-Band Dosing (Children Weighing  $\geq 14$  kg)  
Scored 150-mg Tablet**

Weight	Twice-Daily AM Dose	Twice-Daily PM Dose	Once-Daily Dose
14 kg to <20 kg	½ tablet (75 mg)	½ tablet (75 mg)	1 tablet (150 mg)
$\geq 20$ kg to <25 kg	½ tablet (75 mg)	1 tablet (150 mg)	1½ 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 solid-dosage form.

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

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

- 150 mg twice daily, *or*
- 300 mg once daily

**[Combivir and Generic] Lamivudine plus Zidovudine**

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

- One tablet twice daily

**[Trizivir and Generic] Abacavir plus Lamivudine plus Zidovudine**

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

- One tablet twice daily

**[Epzicom] Abacavir plus Lamivudine**

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

- One tablet once daily

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

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

- One tablet once daily
- For use in patients who are antiretroviral (ARV) treatment-naïve or treatment-experienced (but integrase strand transfer inhibitor-naïve) and who are not being treated with UGT1A1/CYP3A inducers.

### **[Symfi Lo] Efavirenz plus Lamivudine plus TDF**

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

- One tablet once daily on an empty stomach

**Note:** The new fixed-dose combination (Symfi Lo) with a lower dose of efavirenz has not yet been discussed by the Panel. The Panel will address its use in children in a later update.

<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. The Eпивir HBV tablet is appropriate for use in children who require a dose of lamivudine 100 mg for treatment of HIV.

## 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.

## Tenofovir Alafenamide (TAF, Vemlidy) (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: 25 mg<sup>a</sup>**

#### Fixed-Dose Combination Tablets

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

### Dosing Recommendations

#### [Descovy] Emtricitabine plus TAF

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

- *Body Weight 25 to  $<35$  kg:* 1 tablet once daily in combination with other antiretroviral (ARV) agents, except for protease inhibitors (PIs) that require a CYP3A inhibitor (i.e., emtricitabine/TAF [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:* 1 tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

#### [Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

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

- 1 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-1 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 plus Rilpivirine plus TAF

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

- 1 tablet once daily with a meal in ARV-naive patients with HIV-1 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-1 RNA

### 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.
- 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 (see the [Emtricitabine](#), [Elvitegravir](#), [Cobicistat](#), [Rilpivirine](#), and [Bictegravir](#) sections).
- Use of Genvoya is not FDA-recommended with other ARV drugs, but this FDC has safely been used with darunavir.<sup>1</sup> Descovy can be safely used with cobicistat- or ritonavir-boosted darunavir or atazanavir in patients weighing  $\geq 35$  kg.<sup>2</sup>
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs co-formulated 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.

### Metabolism/Elimination

- TAF undergoes renal excretion.

<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.

### **[Biktarvy] Bictegravir plus Emtricitabine plus TAF**

#### ***Pediatric/Adolescent Dose (Aged <18 Years):***

- Biktarvy has not been Food and Drug Administration (FDA) approved for use in patients aged <18 years.
- *Children Aged <12 Years:* No data on appropriate dose of Biktarvy in children aged <12 years.
- *Children/Adolescents (Aged ≥ 12 Years to 18 Years and Weighing ≥ 35 kg):* 1 tablet once daily. This is an **investigational dose**.

#### ***Adult Dose (Aged ≥ 18 Years):***

- 1 tablet once daily in ARV-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months 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.

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

- 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 co-formulations **are not recommended** in patients with estimated CrCl <30 mL/min.
- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but should not be used in patients with severe hepatic impairment because they have not been studied in that group.

<sup>a</sup> TAF 25 mg tablets (Vemlidy) are FDA-approved 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 May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

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

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

#### Fixed-Dose Combination Tablets

- [*Truvada low-strength tablet*]
  - Emtricitabine 100 mg plus tenofovir disoproxil fumarate (TDF) 150 mg
  - Emtricitabine 133 mg plus TDF 200 mg
  - Emtricitabine 167 mg plus TDF 250 mg
- [*Truvada tablet*] Emtricitabine 200 mg plus TDF 300 mg
- [*Atripla*] Efavirenz 600 mg plus emtricitabine 200 mg plus TDF 300 mg
- [*Complera*] Emtricitabine 200 mg plus rilpivirine 25 mg plus TDF 300 mg
- [*Stribild*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg
- [*Symfi Lo*] Efavirenz 400 mg plus lamivudine 300 mg plus TDF 300 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Not Food and Drug Administration-approved or recommended for use in neonates and infants aged <2 years.

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

- 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)
$\geq 35$ kg	7.5 scoops (300 mg)

### Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density<sup>a</sup>

### Special Instructions

- Do not crush tablets; TDF oral powder formulation is available for patients unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix TDF oral powder in 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 regard to food, food requirements vary depending on the other ARV drugs contained

### TDF Tablet Dosing Table for Patients Aged ≥2 Years and Weighing ≥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
≥35 kg	300 mg

#### Adolescent (Weighing ≥35 kg)<sup>a</sup> and Adult Dose:

- TDF 300 mg once daily

#### [Truvada] Emtricitabine plus TDF (FTC/TDF)

*Pediatric Dose:*

#### Truvada Pediatric Dosing Table

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	1 FTC/TDF 100 mg/150 mg tablet
22 kg to <28 kg	1 FTC/TDF 133 mg/200 mg tablet
28 kg to <35 kg	1 FTC/TDF 167 mg/250 mg tablet
≥35 kg	1 FTC/TDF 200 mg/300 mg tablet

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

- 1 FTC/TDF 200 mg/300 mg tablet once daily

#### [Atripla] Efavirenz plus Emtricitabine plus TDF

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

- 1 tablet once daily

#### [Complera] Emtricitabine plus Rilpivirine plus TDF

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

- 1 tablet once daily in treatment-naïve adults with baseline viral load <100,000 copies/mL or virologically suppressed adults who are currently on their first or second regimen and have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.
- Administer with a meal of at least 500 calories.

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

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

- 1 tablet once daily in treatment-naïve adults. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known

in a FDC tablet. Food requirements are listed with dosing recommendations.

- Measure serum creatinine and urine dipstick for protein and glucose before starting a TDF-containing regimen and monitor serum creatinine and urine dipstick 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) has less bone and renal toxicity than TDF, but 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 requiring dialysis.
- The FDC 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.
- Stribild should not be used in patients with severe hepatic impairment.

substitutions associated with resistance to the individual components of Stribild.

- Administer with food.

**[Symfi Lo] Efavirenz plus Lamivudine plus TDF**

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

- 1 tablet once daily

**Note:** The new fixed-dose combination (FDC) Symfi Lo, which has a lower dose of efavirenz, has not yet been discussed by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel). The Panel will address its use in children in a later update.

<sup>a</sup> See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (Sexual Maturity Rating 1 and 2, previously called Tanner staging).

# Zidovudine (ZDV, AZT, Retrovir) (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

**Tablets:** 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 plus zidovudine 300 mg (scored)
- [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

## Dosing Recommendations

**Note:** 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 (Weeks) at Birth<sup>a</sup>

Gestational Age at Birth	Oral Zidovudine Dose								
≥35 Weeks	Birth to Age 4 Weeks: <ul style="list-style-type: none"><li>• 4 mg/kg orally twice daily or alternative simplified weight band dosing</li></ul>								
	<a href="#">Simplified Weight Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth:</a>								
	<b>Note:</b> The doses in this table provide approximately 4 mg/kg orally twice daily from birth to age 4 weeks.								
	<table border="1"><thead><tr><th>Weight Band</th><th>Volume 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>	Weight Band	Volume 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 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								
Aged >4 Weeks: <ul style="list-style-type: none"><li>• 12 mg/kg orally twice daily</li></ul>									

## Selected Adverse Events

- Bone marrow suppression: macrocytosis with or without anemia, neutropenia
- 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.
- For infants unable to tolerate oral agents, the intravenous (IV) dose should be 75% of the oral dose, but the dosing interval should remain the same.
- 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.

Gestational Age at Birth	Oral Zidovudine Dose
≥30 to <35 Weeks	Birth to Age 2 Weeks: • 2 mg/kg orally twice daily  Aged 2 Weeks to 6 to 8 Weeks: • 3 mg/kg orally twice daily  Aged >6 to 8 Weeks: • 12 mg/kg orally twice daily
<30 Weeks	Birth to Age 4 Weeks: • 2 mg/kg orally twice daily  Aged 4 Weeks to 8 to 10 Weeks: • 3 mg/kg orally twice daily  Aged >8 to 10 Weeks: • 12 mg/kg orally twice daily

<sup>a</sup> For premature infants who are diagnosed with HIV, the time to change the dose to continuation dose varies with postgestational age and clinical status of the neonate (see the Special Issues for Neonates section below).

**Note:** For infants who are unable to tolerate oral agents, the intravenous (IV) 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: 180–240 mg/m<sup>2</sup> body surface area every 12 hours

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

- 300 mg twice daily

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

Adolescent (Weighing ≥30 kg) and Adult Dose:

- 1 tablet twice daily

#### [Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet twice daily

## Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

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

- Dose adjustment is required in renal insufficiency.

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

- Dose 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.

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

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

# Efavirenz (EFV, Sustiva) (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:** 50 mg, 200 mg

**Tablets:** 600 mg

### Fixed-Dose Combination Tablets:

- [Atripla] Efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus 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 [tables A1 and A2](#) in the [Pharmacokinetics and Dosing: Infants and Children Aged <3 Years](#) section below). Evaluation of CYP2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring should be used with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure plasma concentration at age 3 years after making the transition to the new dose (see [Therapeutic Drug Monitoring](#) in the text below). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

## Selected Adverse Events

- Rash, which is generally mild and transient and appears to be more common in children than in adults
- Central nervous system symptoms such as fatigue, poor sleeping patterns, **insomnia**, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- False-positive with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- QTc prolongation has been observed with the use of efavirenz. Clinicians should consider using an alternative to efavirenz in patients taking a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

## 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 central nervous system side effects.
- Administer **efavirenz**, Atripla, **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 tablets, see other drug sections in [Appendix A: Pediatric Antiretroviral Drug Information](#) for special instructions and additional information**



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 into 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) because of concern for 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.

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

- Efavirenz 600 mg once daily

### [Atripla] Efavirenz plus Emtricitabine plus TDF

- Atripla should not be used in pediatric patients <40 kg as the dose of efavirenz 600 mg would be excessive.

Adult Dose:

- One tablet once daily

### [Symfi Lo] Efavirenz plus Lamivudine plus TDF: Pediatric (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily

**Note:** The new fixed-dose combination (Symfi Lo), which has a lower dose of efavirenz, has not yet been discussed by the Panel. The Panel will address its use in children in a later update.

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 1–2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer infant formula mixture using a 10-mL syringe.
- After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

### Metabolism/Elimination

- Cytochrome P450 3A (CYP3A) 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 and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are fixed-dose combination products and TDF and emtricitabine require dose adjustment based on renal function, Atripla and Symfi Lo should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.



## Etravirine (ETR, Intelence, TMC 125) (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: 25 mg, 100 mg, and 200 mg

#### Dosing Recommendations

##### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

##### Pediatric Dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

##### Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years and Weighing ≥16 kg

Body Weight	Dose
16 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
≥30 kg	200 mg twice daily

##### Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

#### Selected Adverse Events

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

#### Special Instructions

- Always administer etravirine following a meal. Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
- Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.

##### 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 enough liquid to cover the medication, and stir well until the water looks milky. If desired, add more water or, alternatively, orange juice or milk. **Note:** Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm (>40° C) drinks, 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.

#### Metabolism/Elimination

- Etravirine is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate

for CYP3A4, 2C9, and 2C19.

- 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 necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

Etravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required in patients with renal impairment.

## Nevirapine (NVP, Viramune) (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:** Immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg

**Suspension:** 10 mg/mL

### Generic Formulations

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

**Suspension:** Generic suspension is no longer available in the United States.

**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 directly from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

### Dosing Recommendations

#### Neonate and Infant (Aged $\leq 14$ Days) Dose for Prevention:

- See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#).

#### Pediatric Dose for Treatment of HIV

**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 (see footnote<sup>a</sup> and text below).

#### Immediate Release Tablets and Suspension Formulations

*Aged  $< 1$  Month (This **Investigational Dose** is Not Food and Drug Administration-Approved):*

- 34–37 weeks gestational age: Nevirapine 4 mg/kg/dose twice daily for the first week, increasing to nevirapine 6 mg/kg/dose twice daily thereafter (no lead in; please see text and footnote<sup>a</sup>)
- $\geq 37$  weeks gestational age to age  $< 1$  month: Nevirapine 6 mg/kg/dose twice daily (no lead in; please see text and footnote<sup>a</sup>)
- See the Special Considerations for Dosing: Neonates and Premature Infants section below.

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

- 200 mg/m<sup>2</sup> of body surface area (BSA)/dose twice daily after lead-in dosing.<sup>a</sup> In children aged  $\leq 2$  years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

### 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.
- 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 the Major Toxicities section below).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for more than 14 days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see the Dosing Considerations: Lead-In Requirement section 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 the Major Toxicities section below).

### Aged $\geq 8$ Years:

- 120–150 mg/m<sup>2</sup> BSA/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 is left static to achieve the appropriate mg-per-m<sup>2</sup> dose as the child grows, as long as there are no untoward effects.

BSA Range	NVP XR
0.58 m <sup>2</sup> to 0.83 m <sup>2</sup>	200 mg once daily (2 x 100 mg)
0.84 m <sup>2</sup> to 1.16 m <sup>2</sup>	300 mg once daily (3 x 100 mg)
$\geq 1.17$ m <sup>2</sup>	400 mg once daily (1 x 400 mg)

**Key to Abbreviations:** BSA = body surface area; NVP XR = nevirapine extended release

### Extended-Release Formulation

#### Aged $\geq 6$ Years:

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

#### Adolescent and Adult Dose: <sup>a,b</sup>

- 200 mg twice daily or 400 mg extended release once daily **after lead-in dosing**.

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

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

- Nevirapine **should not be co-administered to patients receiving atazanavir (with or without ritonavir)**.
- Nevirapine increases the metabolism of lopinavir. A dose adjustment of lopinavir is recommended (see [Lopinavir/Ritonavir](#)).

### Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% of nevirapine dose is excreted in urine (glucuronidated metabolites).

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

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

#### 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 and increased in a stepwise fashion to allow for induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the age-appropriate dose of the immediate-release formulation once daily (half-daily dose) for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate full dose, administered twice daily, of the immediate-release preparation. However, in children aged  $\leq 2$  years, some experts initiate nevirapine without a lead-in (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving full-dose, immediate-release nevirapine, extended-release tablets can be used without the 200-mg 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 1 form of nevirapine at the same time. 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 May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

Tablet: 25 mg

#### Fixed-Dose Combination Tablet:

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

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

#### Children Aged <12 Years:

- Not Food and Drug Administration-approved for use in children aged <12 years. For more information regarding consideration for use in children aged <12 years and weighing  $\geq 35$  kg, see the Pharmacokinetics section below.

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

- 25 mg once daily in antiretroviral (ARV)-naive patients who have HIV RNA  $\leq 100,000$  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.

#### Combination Tablets

[Complera] Emtricitabine plus Rilpivirine plus TDF

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

- One tablet once daily in treatment-naive patients with baseline viral load  $\leq 100,000$  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 (HIV-1 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 Complera.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

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

- One tablet once daily with a meal as initial therapy in treatment-naive patients with

### 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.
- Use rilpivirine with caution when co-administered 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 additional information about the individual components of the FDC.

HIV-1 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-1 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.

#### **[Juluca] Dolutegravir plus 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-1 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 children or adolescents. See Simplification of Treatment section below.

## **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 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 effects 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)

Fosamprenavir (FPV, Lexiva)

Indinavir (IDV, Crixivan)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Nelfinavir (NFV, Viracept)

Saquinavir (SQV, Invirase)

Tipranavir (TPV, Aptivus)



# Atazanavir (ATV, Reyataz) (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 Packet:** 50 mg/packet

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

**Fixed-Dose Combination Tablets**

- [Evo<sup>®</sup>taz] Atazanavir 300 mg plus cobicistat 150 mg

## Generic Formulations

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

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

## Dosing Recommendations

### Neonate Dose:

- 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).

### Pediatric Dose

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

- Powder formulation must be administered with ritonavir.
- Not approved for use in infants aged <3 months or weighing <5 kg.

### Infants and Children (Aged ≥3 Months; Weighing ≥5 kg)

#### Atazanavir Powder<sup>a</sup>

Weight (kg)	Once-Daily Dose
5 kg to <15 kg	Atazanavir 200 mg (4 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 (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

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

- 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 (primarily with ritonavir boosting)

## Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets are not interchangeable.
- Do not open capsules.

### Powder Administration:

- Mix atazanavir oral powder with at least 1 tablespoon of 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.
- Because atazanavir can prolong the



## Children (Aged ≥6 Years; Weighing ≥15 kg):

### Atazanavir Capsules<sup>a</sup>

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

#### For Treatment-Naive Pediatric Patients Who Do Not Tolerate Ritonavir:

- Atazanavir powder must be administered with ritonavir.
- For capsule formulation, atazanavir/ritonavir (ATV/r) is preferred for children and adolescents. Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted atazanavir in children aged <13 years. 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](#)).
- Only ATV/r should be used in combination with tenofovir disoproxil fumarate (TDF), because TDF decreases atazanavir exposure.

### Adolescent and Adult Dose

#### Treatment-Naive Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children 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](#)).

#### Treatment-Experienced Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children aged <18 years.

electrocardiogram PR interval, use atazanavir with caution in patients with pre-existing cardiac conduction system disease or with other drugs 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, special dosing information is indicated (see the Drug Interactions section on the [atazanavir package insert](#)). When administered with buffered didanosine formulations or antacids, give atazanavir at least 2 hours before or 1 hour after antacid or didanosine administration.
- The plasma concentration, and therefore the therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is co-administered with proton-pump inhibitors. Antiretroviral therapy-naive patients receiving proton-pump inhibitors should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted atazanavir. Co-administration of atazanavir with proton-pump inhibitors is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at 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 contains 35 mg of phenylalanine.

### Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).

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

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

*Atazanavir in Combination with Efavirenz (Adults) in Treatment-Naive Patients Only:*

- Atazanavir 400 mg plus ritonavir 100 mg plus efavirenz 600 mg, all once daily at separate times.<sup>d</sup>
- Although ATV/r should be taken with food, efavirenz should be taken on an empty stomach, preferably at bedtime. Efavirenz should not be co-administered with atazanavir (with or without ritonavir) in treatment-experienced patients, because efavirenz decreases atazanavir exposure.

*Atazanavir in Combination with TDF (Adults):*

- Atazanavir 300 mg plus ritonavir 100 mg plus TDF 300 mg, all once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg plus TDF 300 mg, all once daily with food. **Atazanavir/cobicistat** is currently not **FDA-approved** for use in children aged <18 years.
- Only boosted atazanavir should be used in combination with TDF, because TDF decreases atazanavir exposure.

severe hepatic impairment.

Atazanavir Dosing in Patients with Renal Impairment:

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

<sup>a</sup> mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability was higher for the capsules than for the powder when studied in adults.

<sup>b</sup> For a child weighing  $\geq 25$  kg who cannot swallow atazanavir capsules, atazanavir 300 mg (6 packets) oral powder plus ritonavir 100 mg oral solution, both once daily with food, may be used.

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

<sup>d</sup> For adult patients who cannot swallow capsules, atazanavir oral powder is taken 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 May 22, 2018; last reviewed May 22, 2018)

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, and 800 mg

### Fixed-Dose Combination Tablets

- [Prezcobix] Darunavir 800 mg plus cobicistat 150 mg

## Dosing Recommendations

**Note:** Darunavir should not be used without a pharmacokinetic (PK) enhancer (i.e., boosting agent): ritonavir (for children and adults) or cobicistat (for adults only).

### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

### Pediatric Dose

*Aged <3 Years:*

- **Do not use darunavir in children aged <3 years or weighing  $\leq 10$  kg** because of toxicity concerns based on seizures and death observed in infant rats and attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

*Aged  $\geq 3$  Years:*

- See table below for children aged  $\geq 3$  years who are antiretroviral **treatment-naive and treatment-experienced** with or without 1 or more darunavir resistance-associated mutations.

### Aged 3 to <12 Years and Weighing $\geq 10$ kg

Weight (kg)	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</sup> ) <sup>e</sup> plus ritonavir (100 mg tablet or 1.25 mL <sup>b</sup> )
$\geq 40$ kg	Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

## Selected Adverse Events

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

## Special Instructions

- In patients with 1 or more darunavir-associated mutations, darunavir should only be used twice daily. **Darunavir resistance-associated mutations are:** V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- Darunavir must be administered with food, which increases plasma concentrations by 30%.
- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses for each weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important.
- Store darunavir tablets and oral suspension at room temperature (25°C or 77°F). Suspension must be shaken well before dosing.

## Metabolism/Elimination

- Cytochrome (CYP) P450 3A4 inhibitor and substrate.

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

**Adolescent (Weighing  $\geq 40$  kg)<sup>e</sup> and Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations)**

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

**Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations):**

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

**Adolescent (Weighing  $\geq 30$  to <40 kg; Treatment Naive or Treatment-Experienced with or without at Least 1 Darunavir Resistance-Associated Mutation):**

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

**Adolescent (Weight  $\geq 40$  kg) and Adult Dose (Treatment-Experienced With at Least 1 Darunavir Resistance-Associated Mutation):**

- 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.

<sup>a</sup> Once-daily dosing is Food and Drug Administration (FDA)-approved, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend it for children (see Frequency of Administration section below).

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

<sup>c</sup> Ritonavir 80 g/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 (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 **cobicistat section** for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

**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 [CrCl] 30–60 mL/min).

# 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 (≥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.

## Lopinavir/Ritonavir (LPV/r, Kaletra) (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:

- [Kaletra] Lopinavir 80 mg plus 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 plus ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg plus ritonavir 50 mg

### Dosing Recommendations

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

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days due to potential toxicities.

#### Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

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

- Once-daily dosing **is not recommended**.
- Lopinavir/ritonavir (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:** 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.

##### Pediatric 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 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

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- 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 (25° C) if used within 2 months. If kept refrigerated (2° C to 8° C or 36° F to 46° F), LPV/r oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing **is not recommended**



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)-naïve 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/Ritonavir 100 mg/25 mg Pediatric Tablets for 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>		
<b>15 kg to 20 kg</b>	2	2
<b>&gt;20 kg to 25 kg</b>	3	2
<b>&gt;25 kg to 30 kg</b>	3	3
<b>&gt;30 kg to 35 kg</b>	4 <sup>a</sup>	3
<b>&gt;35 kg to 45 kg</b>	4 <sup>a</sup>	4 <sup>a</sup>
<b>&gt;45 kg</b>	4 <sup>a</sup> or 5 <sup>b</sup>	4 <sup>a</sup>

<sup>a</sup> Four of the LPV/r 100 mg/25 mg tablets can be substituted with two tablets each containing LPV/r 200 mg/50 mg in children capable of swallowing a larger tablet.

<sup>b</sup> In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, weighing >45 kg, 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 Dose (Aged >18 Years):

- 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 or adolescents, or in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special

because of considerable variability in plasma concentrations in children aged <18 years and a higher incidence of diarrhea.

- Use of LPV/r once daily is specifically **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 P (CYP) 3A4 inhibitor and substrate.

#### 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 co-formulation 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.

Instructions for list).

In Patients 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**.

*Pediatric Dose (Aged >12 Months to 18 Years):*

- 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 Dose (Aged >18 Years):*

- 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 Saquinavir Hard-Gel Capsules or in Combination with Maraviroc:

- Saquinavir and maraviroc doses may need modification (see the [Saquinavir](#) and [Maraviroc](#) sections for more information). **The combination of saquinavir and LPV/r is not recommended.**

## 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**.

## 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.

## Entry and Fusion Inhibitors

Enfuvirtide (T-20, Fuzeon)

Maraviroc (MVC, Selzentry)



## 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**

- Catabolism to constituent amino acids.

# Maraviroc (MVC, Selzentry) (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:** 25 mg, 75 mg, 150 mg, and 300 mg

**Oral Solution:** 20 mg/mL

## Dosing Recommendations

### Neonate and Infant Dose:

- Not approved for use in neonates or infants

### Pediatric Dose:

- Approved 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	Liquid 20 mg/mL	Tablets
When given with potent cytochrome P (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including elvitegravir/ritonavir (EVG/r) and 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	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
>40 kg	150 mg	7.5 mL	One 150-mg tablet
When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers:			
10 kg to <20 kg	Not recommended		
20 kg to <30 kg	Not recommended		
30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
>40 kg	300 mg	15 mL	One 300-mg tablet
When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor):			
Children in all weight bands	Not recommended		

## 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 patients with only CCR5-tropic HIV-1. Conduct testing with HIV tropism assay (see [Drug-Resistance Testing](#) in the [Adult and Adolescent 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

- Cytochrome P450 3A4 (CYP3A4) substrate

### Maraviroc Dosing in Patients with Hepatic Impairment:

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

### Recommended Adult Maraviroc Dose: Tablets

When Co-Administered With:	Dose
Potent CYP3A inhibitors (with or without a potent CYP3A inducer) including PIs (except TPV/r) and EVG/r	150 mg twice daily
NRTIs, enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
Potent CYP3A inducers, including efavirenz and etravirine (without a potent CYP3A inhibitor)	600 mg twice daily

### Maraviroc Dosing in Adolescents and Adults with Renal Impairment:

- Refer to the manufacturer's prescribing information.
- Data are insufficient to make dosing recommendations for use of maraviroc in children concomitantly receiving noninteracting medications and weighing <30 kg or in all children concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor.

## **Integrase Inhibitors**

Bictegravir (BIC)

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

## Bictegravir (BIC) (Last updated May 22, 2018; last reviewed May 22, 2018)

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.

#### Fixed-Dose Combination Tablet:

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

### Dosing Recommendations

#### [Biktarvy] Bictegravir plus Emtricitabine plus TAF

##### *Pediatric/Adolescent Dose (Aged <18 Years):*

- Biktarvy has not been Food and Drug Administration-approved for use in patients aged <18 years.
- *Children Aged <12 Years:* No data on appropriate dose of Biktarvy in children age <12 years.
- *Children and Adolescents (Aged ≥12–18 Years and Weighing ≥35 kg):* 1 tablet once daily. This is an **investigational dose**.

##### *Adult Dose (Aged ≥18 Years):*

- 1 tablet once daily in ART-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months 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

#### TAF-Associated Adverse Events:

- Increases in low-density lipoprotein cholesterol and total cholesterol levels

### Special Instructions

- Administer with or without food.
- Screen patients for hepatitis B virus (HBV) infection before use of emtricitabine or TAF. Severe acute exacerbation of HBV can occur when emtricitabine or TAF is discontinued; therefore, monitor hepatic function for several months after halting therapy with emtricitabine or TAF.
- Biktarvy is not recommended for use with other ARV drugs.
- See the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for special instructions and additional information about the individual drug components of Biktarvy.

### Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P (CYP) 450 3A and uridine diphosphate glucuronosyltransferase (UGT) 1A1.
- Refer to the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for more information on these components of Biktarvy.

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

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

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

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

## Dolutegravir (DTG, Tivicay) (Last updated May 22, 2018; last reviewed May 22, 2018)

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:**

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

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for use in neonates/infants

#### Pediatric Dose (Weighing <30 kg):

- Not approved for children weighing <30 kg
- Clinical trials in children with HIV weighing <30 kg are under way (see text).

#### Pediatric Dose (Weighing ≥30 kg to <40 kg)

Body weight	Dose <sup>a</sup> (mg/day)	Dosing Frequency	Tablet Size (mg)
30 kg to <40 kg	35	Once daily	One 10-mg tablet plus one 25-mg tablet

<sup>a</sup> These doses are for children who are treatment-naïve or treatment-experienced (but integrase strand transfer inhibitor [INSTI]-naïve) and who are not being treated with UGT1A1/CYP3A inducers.

**Note:** Dolutegravir 10-mg and 25-mg tablets may be available in retail pharmacies. If dolutegravir 10-mg or 25-mg tablets must be ordered, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GlaxoSmithKline (GSK) distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

### 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
- Hypersensitivity reactions, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported rarely.

### Special Instructions

- May be taken without regard to meals
- 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-, 25-, 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 semi-solid food or liquid, all of which should be consumed **immediately**.<sup>1</sup>
- The efficacy of 50-mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).
- 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.



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

Population	Recommended Dose
Treatment-naive or treatment-experienced/INSTI-naive	50 mg once daily
Treatment-naive or treatment-experienced/INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance <sup>a</sup>	50 mg twice daily

<sup>a</sup> Combinations that do not include metabolic inducers should be considered where possible.

### [Triumeq] Abacavir plus Dolutegravir plus Lamivudine

#### *Pediatric (Weighing $\geq 40$ kg) and Adult Dose:*

- 1 tablet once daily
- For use in patients who are antiretroviral (ARV) treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers
- See [Abacavir](#) section for special instructions about testing for abacavir hypersensitivity.

### [Juluca] Dolutegravir plus Rilpivirine

#### *Adult Dose:*

- 1 tablet once daily with a meal as a complete regimen to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA  $< 50$  copies/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 children or adolescents. See Simplification of Treatment section below.

## Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate. **Drugs that induce these enzymes and transporters may decrease plasma concentrations of dolutegravir.**

### Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of lack of data, dolutegravir is not recommended in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect 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 May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Tablet:** Discontinued by the manufacturer. Only available in fixed-dose combination tablets.

#### Fixed-Dose Combination Tablets:

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

### Dosing Recommendations

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

##### *Pediatric (Weighing <25 kg) Dose:*

- No data on appropriate dose of elvitegravir in *Genvoya* for children weighing <25 kg

##### *Child and Adolescent (Weighing ≥25 kg; Any Sexual Maturity Rating [SMR]) and Adult Dose:*

- One tablet once daily

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

##### *Pediatric (Weighing <35 kg) Dose:*

- No data on appropriate dose of elvitegravir in *Stribild* for children weighing <35 kg

##### *Adolescent (Weighing ≥35 kg and SMR 4 or 5) and Adult Dose:*

- One tablet once daily

**Note:** *Stribild* and *Genvoya* are Food and Drug Administration approved for use in ARV treatment-naïve patients or to replace the current ARV regimen in patients who are virologically suppressed (HIV-1 RNA <50 copies/mL) on at 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:

- Renal insufficiency
- Decreased bone mineral density
- Flatulence

#### Cobicistat-Specific Adverse Events:

- Alteration in tubular secretion of creatinine

#### Genvoya-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

#### TAF-Associated Adverse Events:

- Increased low-density lipoprotein-cholesterol and total cholesterol

#### Cobicistat-Associated Adverse Events:

- Alteration in tubular secretion of creatinine

### Special Instructions

- Administer with food.
- When using *Stribild*, which contains TDF, monitor estimated creatinine clearance (CrCl),

urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine  $>0.4$  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 therapy with emtricitabine, TDF, or TAF is stopped.
- Neither Stribild nor Genvoya is recommended for use with other antiretroviral (ARV) drugs.

### **Metabolism/Elimination**

- Elvitegravir is metabolized by cytochrome P (CYP) 450 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 in the guidelines for further details.
- 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 because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl  $<30$  mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

## Raltegravir (RAL, Isentress) (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:** 400 mg (film-coated poloxamer tablet)

**HD Tablets:** 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

See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12. Newborn Antiretroviral Dosing Recommendations](#) for prevention of perinatal transmission.

#### Neonate Dose:

Neonates  $\geq$  37 Weeks of Gestation (Weighing  $\geq$  2 kg):

- No dosing information is available for preterm or low birthweight infants.

#### Oral Suspension Dosing Table

Full-Term Neonates (Birth to 4 Weeks [28 Days] of Age):

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

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

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

### 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

- Can be given without regard to food.
- Co-administration or staggered administration of aluminum- 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 co-administered:** 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**.
- 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 preparations.
- Chewable tablets should be stored in the

## Infant and Pediatric Dose

### Oral Suspension Dosing Table<sup>a</sup>

Children Aged  $\geq 4$  Weeks and Weighing  $\geq 3$  kg to  $< 20$  kg:

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

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

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

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

### Pediatric Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

Children Weighing  $\geq 11$  kg:

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

**Child and Adolescent Weighing  $\geq 50$  kg (HD), see Pediatric Use, Approval:**

- 1200 mg (two 600 mg HD) once daily
- For treatment-naïve or virologically suppressed patients on an initial regimen of 400 mg twice daily.

Body Weight (kg)	Dose	Number of Chewable Tablets
11 to $< 14$	75 mg twice daily	3 X 25 mg twice daily
14 to $< 20$	100 mg twice daily	1 X 100 mg twice daily
20 to $< 28$	150 mg twice daily	1.5 X 100 mg <sup>b</sup> twice daily
28 to $< 40$	200 mg twice daily	2 X 100 mg twice daily
$\geq 40$	300 mg twice daily	3 X 100 mg twice daily

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

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

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

original package with desiccant to protect them from moisture.

- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided in kits that include mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions 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 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 for standard-dose raltegravir in patients with mild-to-moderate hepatic insufficiency. No dosing studies of raltegravir HD have been done 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 necessary in patients with any degree of renal impairment.

## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

# Cobicistat (COBI, TYBOST) (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:** 150 mg

### Fixed-Dose Combination Tablets:

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

## Dosing Recommendations

### Cobicistat is a Pharmacokinetic (PK) Enhancer:

- The only use of cobicistat is as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and selected integrase inhibitors. Cobicistat **is not interchangeable** with ritonavir. See dosing information for [elvitegravir](#) and specific [PIs](#) that require cobicistat for boosting.

### Pediatric Dosing

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

- Cobicistat alone (as Tybost)
- Evotaz
- Prezcobix
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV regard the above agents as potentially appropriate for use in select children aged <18 years and weighing  $\geq 35$  kg. An expert in pediatric HIV infection should be consulted.

*Not FDA-Approved for Use in Children Aged <6 Years or Weighing <25 kg:*

- Genvoya

*Not FDA-Approved for Use in Children Aged <12 years Weighing <35 kg:*

- Stribild

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

- Cobicistat 150 mg orally once daily as a component of Genvoya

## Selected Adverse Events

- When co-administered with TDF, cobicistat may be associated with higher risk of renal tubular adverse events than ritonavir.

## Special Instructions

- Cobicistat **is not interchangeable** with ritonavir.
- **Do not administer** cobicistat with ritonavir or with drugs containing cobicistat.
- Not recommended for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir in combination with a PI) because no data are available.
- Use with PIs other than atazanavir 300 mg or darunavir 800 mg administered once daily is not recommended because no data are available on other combinations or doses.
- Patients with a confirmed increase in serum creatinine  $>0.4$  mg/dL from baseline should be closely monitored for renal safety.
- When used in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see [Table 15i](#)). In patients at risk of renal impairment, also monitor serum phosphate.
- When used in combination with other ARV drugs, see those specific sections of the appendix ([atazanavir](#), [darunavir](#), [elvitegravir](#), [TDF](#), [TAF](#)).

## Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor



**Adolescent (Weighing  $\geq$ 35 kg and SMR 4 or 5)  
Dose:**

- Cobicistat 150 mg orally once daily as a component of Stribild

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

- Cobicistat must be administered as:
  - The combination tablets Stribild or Genvoya, in which case it would not be dosed with any other antiretroviral (ARV) drugs; *or*
  - The tablet Tybost co-administered with atazanavir or darunavir at the doses listed in the table below and at the same time, in combination with other ARV drugs; *or*
  - Combination tablets with atazanavir (Evotaz) or darunavir (Prezcobix), with food, and in combination with other ARV drugs.

Cobicistat Dose	Co-Administered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild or Genvoya; no other ARV drugs needed	Treatment-naive or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya
150 mg orally once daily	Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (coformulated as Prezcobix or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naive or treatment-experienced with no darunavir-associated resistance mutations

- P-glycoprotein and breast cancer resistance protein inhibitor
- Cobicistat inhibits renal tubular secretion of creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

**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 because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl  $<$ 30 mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

## Ritonavir (RTV, Norvir) (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 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

### 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 ritonavir dosing 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.

### Selected Adverse Events

- Gastrointestinal intolerance, nausea, vomiting, diarrhea
- Paresthesia (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

### Special Instructions

- Administer ritonavir with food to increase absorption and reduce gastrointestinal adverse effects.
- Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- 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 within 2 hours of mixing.

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

- Mix 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 food allergy history before making these recommendations.
- Counsel parents or patients that the bad taste will not be completely masked.

#### Metabolism/Elimination

- Cytochrome P (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.

#### 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. Data are unavailable 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).